

CLINICAL AND PATHOLOGICAL

PAPERS

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W. T. HOWARD, M.D.

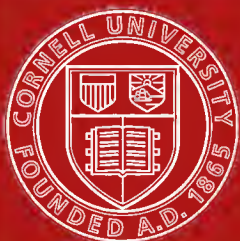
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PART 1
CLINICAL PAPERS

Gastric Ulcer

By C. F. HOOVER, M. D., Cleveland.

Rational treatment of gastric ulcer must be based on a careful consideration of the pathogenesis of the ulcer and the attending alterations of motor and secretory functions of the stomach.

To imply from this prefatory remark that the pathogenesis of peptic ulcer is understood, would surpass our present knowledge of the subject, but we can determine clinically whether we are dealing with a peptic, perforating ulcer or with an ulcer of some other origin. The synonyms employed in most of our textbooks supply the attributes which serve to differentiate this ulcer from all others, viz., simple, round, peptic, perforating. The ulcer occurs singly as a rule. It is accompanied by an exalted secretory function of the glandular mucosa and is therefore a peptic, or chloropeptic ulcer; and it is a perforating ulcer because it is very refractory to the healing process.

Both clinical and experimental knowledge confirm this differentiation of the peptic ulcer from ulcers of other origin. Clairmont's¹ series of experiments serve to show the readiness with which the gastric mucosa will heal provided the injury occurs in a stomach which has a normal musculature and normal mucosa. Clairmont produced ulcers in the stomachs of dogs by dissecting off one cm. square of the mucous membrane, then burning the base of the ulcer with acid and finally ligating the arteries and veins in the vicinity of the ulcer. In spite of this severe treatment the ulcers healed in about three weeks and in most instances the site of the ulcer showed no histological differences from other portions of the gastric mucosa. So complete was the reproduction of the glandular mucosa that microscopically the site of the former ulcer could not be determined. The same result followed in another series of experiments in which gastro-enterostomy was performed at the same time the ulcer was produced. Clairmont makes the following deductions: 1. That to the present time no one has been able to produce a genuine ulcer, i. e. loss of mucosa without tendency to heal, as all these cases tended to heal. 2. In the cardiac portion these artefacts heal more promptly than in the pyloric region. In the cardia, healing occurs within three weeks, whereas in the pylorus healing requires about six or seven weeks. 3. That healing is unmodified by gastro-enterostomy, early or late, and the statement that gastro-enterostomy trans-

forms an ulcer to the status of an open wound, i. e. changes an unhealing loss of substance to a healing loss of substance is refuted.

Clinically we find that gastric ulcers of traumatic origin heal very promptly without any of the pain and alterations in the motor or secretory functions of the stomach. It is very doubtful if trauma alone will account for any round ulcer of the stomach. When gastric ulcer persists for a long time after an injury, it is presumed that the injury must be accompanied by hyperchlorhydria. When the ulcer is not tuberculous or syphilitic or of the peptic variety we know from an abundant clinical experience, that recovery is prompt without the aid of any treatment, even when a liberal diet is resumed before an erosion could possibly heal. By this statement I do not wish to be understood as advocating an unrestricted diet in such cases; but as soon as the bleeding ceases the patient can be given vegetable puré, scraped meat, eggs and milk. If this diet is tolerated without any distress and the injury has occurred in a stomach previously healthy, a liberal diet can be safely given at the end of a week. Erosions of the gastric mucosa are sometimes traceable to circulatory disease, but in such cases healing takes place very promptly as in traumatic cases. When dyspepsia, pain and hemorrhage occur in elderly persons with arteriosclerosis we must not assume that the dyspepsia and pain result from the erosion which has caused the bleeding. The erosion in such cases is merely a pathological symptom due to the vascular disease. The pain, stasis of chyme, and vomiting are caused by the altered blood circulation in the stomach, and are not caused by erosion. These cases of sclerosis of the gastric arterial supply often lead to a false diagnosis of ulcer or carcinoma, on account of bleeding which attends the symptoms of secretory and motor defects. The pain may be intense, but it is not caused by the accompanying erosion but by the spasm of the gastric wall, the pylorus and cardia, a clinical symptom to which the term intermittent claudication has been applied, on account of its analogy with the symptoms which occur in the extremities of patients suffering from arterial disease. Such a patient suffering from bleeding, pain and vomiting would require treatment directed toward relief of the splanchnic circulation. The erosion can be disregarded as a serious factor.

I dare say that many of us can recall instances of elderly patients in whom the symptoms of dyspepsia and hemorrhage sug-

gested a diagnosis of carcinoma or ulcer and the patients lived long enough afterward to disprove the diagnosis.

Hematemesis occurs rarely in acute infectious disease such as typhoid and pneumonia. When such erosions, due to bacterial growths in the mucosa, as has been shown by Daculafoy², do occur, the patients do not suffer from the gastric erosions; the stomach distress is caused by the general infection. I have had only one such experience with a typhoid patient. The patient recovered from the typhoid after an illness of six weeks. Profuse hematemesis occurred in the beginning of the second week of the disease but there were no more gastric symptoms than one ordinarily sees in the course of typhoid fever. The feeding of the patient was not interrupted.

I had a similar experience with an elderly woman during an attack of lobar pneumonia which proved fatal on the tenth day of the disease. Severe hematemesis occurred on the fifth day of the pneumonia, but there were no symptoms which could be ascribed to an erosion of the stomach mucosa and the diet was not modified on account of the hemorrhage. Exactly the same experience, with lack of other symptoms than hemorrhage, occurs after abdominal operations.

Although I do not wish to lay down any rules for the treatment of hematemesis, I think our clinical experience shows that when vomiting of blood is the only symptom which can be ascribed to an erosion of the gastric mucosa in traumata, infections and diseases of the vascular supply of the stomach, we can with safety disregard the erosion so far as any direct treatment of the stomach ulcer is concerned. Under such circumstances it is not the erosion which requires treatment, but the basic disease which caused the erosion should enlist our therapeutic efforts.

Ulcerations of the stomach, which demand treatment as ulcers, can be divided into three groups. I am compelled to make this classification from my own clinical experience and, so far as I am able to learn from the literature on the subject, it seems very probable that this classification may form a good working-basis for the care of chronic disease of the stomach associated with ulceration. These three groups are: first, syphilis; second, chronic peptic ulcer in patients who show no signs of congenital asthenia; and third, chronic peptic ulcer occurring in patients with congenital asthenia.

Syphilis must not be forgotten in any case of gastric ulcer. When there is any history or objective sign which suggests the possibility of syphilis, potassium iodid and mercury should both be employed. A very striking fact in syphilis of the stomach is the tolerance for only small doses of the iodid of potash. This was clearly illustrated in one patient who came under my observation six years ago. This man had syphilis 18 years prior to the time of his stomach symptoms. The stomach was greatly dilated, the lower border reaching to within two inches of the symphysis pubis. There was retention of chyme and poracous vomiting. The patient was greatly emaciated. With only three grains of potassium iodid thrice daily, the lower border of the stomach gradually rose to the level of the umbilicus. Within six months the stomach regained its normal dimensions and the patient was able to eat a liberal mixed diet without any distress. During the entire period of the treatment, which lasted several months, this patient was unable to take more than five grains of potassium iodid three times a day. This patient had, I believe, a gumma at the pylorus, but in another case of syphilitic ulcer of the pylorus attended with severe pain, hemorrhage and retention of chyme. with normal gastric acidity, I had the same experience. Only small doses of potassium iodid were tolerated but the results were very satisfactory. The pain, bleeding and stasis of chyme were all relieved. I have had experience with five cases of syphilis of the stomach and in every case the amount of potassium iodid tolerated was very small. The results of treatment were very satisfactory in four of the patients in spite of the small doses of the iodid. In only two of the five patients was mercury used during the period of improvement, so it seems reasonable to assume that in syphilis of the stomach small doses of potassium iodid are successful. I mention this fact because one might be discouraged in the treatment of a case of suspected syphilitic ulcer of the stomach if the patient showed an intolerance of potassium iodid in moderate doses. If in the case of severe pyloric obstruction above mentioned the patient had been given his potassium iodid in the usual way of increasing the dose by one drop daily, the intolerance of the iodid would have manifested itself very early in the treatment and the idea of the lesion being syphilitic would have been abandoned. The possibility of an ulcer being syphilitic should always be very carefully eliminated before the usual treatment for peptic ulcer is employed. This is particularly true in

married women, because they rarely give a history of syphilis. If the infection has been imparted by a conception there may be nothing but the therapeutic test to show the character of the ulcer. This can be accomplished with such small doses of potassium iodid, and within so short a time, that there can never be any good excuse for neglecting the possibility of syphilis. The importance of this measure has been strongly impressed on me by my own experience and by the unfortunate experience of a surgical colleague who performed a pylorectomy with a fatal result; in this case the histological examination revealed the syphilitic character of the disease. The operation could have been avoided and the patient's life saved had the possibility of syphilis been seriously considered.

Given a case of chronic or acute peptic ulcer, what shall be the method of procedure in our therapy? I think we can best arrive at our goal by considering the several symptoms of ulcer.

Hemorrhage is rarely fatal in gastric ulcer. I have never seen a fatal hemorrhage from a simple round ulcer of the stomach. The only fatal case of hematemesis from ulcer which I have seen occurred very early in my experience as a hospital physician and this case proved at autopsy to be one of multiple ulcers situated in the fundus and pylorus; the pathologist made a diagnosis of multiple syphilitic ulcer. Gelatin, in tablespoonful doses, of a 5% sterile solution, every two hours, is recommended and I have used it. How much service it renders seems doubtful. The bleeding is not due to a lack of fibrin-ferment in the blood. If hemorrhage persistently recurs it must be due to the destructive progress of the ulcer. How the styptic property of gelatin can prevent bleeding from a progressing ulcer seems difficult to understand.

Adrenalin is a rational drug to employ. If its styptic property is applied to the ulcer it will certainly be of more service than gelatin and it has the additional property of diminishing the secretion of gastric juice. Another very serviceable feature of adrenalin is the property it has of lessening the muscular activity of the stomach and esophagus.

So far as physiological experiments go, adrenalin should be the most efficient remedy we can employ. Inhibition of the muscular and glandular activity of the stomach and contraction of the arterioles certainly offer all that could be wished for in the treatment of a bleeding gastric ulcer. The dosage is one-half to one oz. drachm of a 1:1000 solution in 2 oz. of water. The use of

ice pills certainly has none of these properties. The muscular activity and glandular secretion persist in a fasting stomach and thus offer very serious obstacles to procuring the quiet which is desirable for a bleeding ulcer.

Should the bleeding be severe an ice bag on the stomach is commonly applied. Why this should be done is not perfectly clear. The application of cold over the epigastrium is one of the means we employ to excite gastric peristalsis, as a means of determining the size of the stomach in making a clinical examination. If a stomach is dilated or prolapsed and we wish to accurately define its outline we pour ether over the epigastrium or stroke the region with a cloth wet in ice water. I know of no evidence that the application of cold will allay gastric peristalsis and there is an abundance of daily clinical experience which shows that cold applied to the epigastrium has decidedly the opposite effect. If the patient is very much agitated a hypodermic injection of morphin may be employed, but it is advisable to learn about the patient's tolerance of morphin before using it. In many persons the sedative effects of morphin are followed by nausea and vomiting of a large amount of thin green liquid. This is of course undesirable, but if there is a history of the drug being well tolerated it will render good service by producing rest for the patient.

When the bleeding is severe all solids and liquids should be withheld, and water given by enemata to allay thirst.

Pain: What can be done for the alleviation of pain? The only drug I have employed for local anesthesia is orthoform given in seven grain doses, three or four times daily when the stomach is empty. Orthoform can be of service only when the point of irritation which causes pain is accessible from the inner surface of the stomach. The pain which originates from perigastritis, perigastric adhesions and spasm of the stomach wall are, of course, unaffected by orthoform.

When a protective coating to the surface of the ulcer is desired for the alleviation of pain, bismuth subnitrate or bismuth carbonate, in amounts of 30 to 60 grs. suspended in a sufficient amount of water to make a fairly thick mixture, can be given. The patient is directed to occupy either the prone or dorsal position so that the bismuth will be applied to the surface of the ulcer. There is a disadvantage in employing bismuth preparations on account of the dark color it gives the stool, which may thus cause some difficulty in recognizing the presence of blood. A cheaper

preparation, and one which does not color the stool, is equal parts of prepared chalk and talcum, one half to a full teaspoonful is given in about three ounces of water before taking food; when the pain is intense opiates are, of course, administered. Hot applications in the form of turpentine stupes serve to arrest the pain, to keep the patient quiet in one position and probably to retard the muscular activity of the stomach, according to Penzoldt.³

Fleischer⁴ found in healthy persons that the application of heat also shortened the requisite period for emptying the stomach. If heat allays muscular spasm and facilitates the emptying of the stomach, then there are good reasons for preferring heat to cold as an external application.

The retention of chyme, hyperchlorhydria and gastrosuccorrhoea may be the chief source of pain in gastric ulcer. Indeed this may be the case when there is a bleeding ulcer and yet the ulcer may not be directly the source of any discomfort. If the precaution is taken to relieve these disturbances in the motor and secretory functions of the stomach, a patient can be made quite comfortable, provided there is no perigastritis. When the ulcer is in a progressive phase (and consequently causing repeated hemorrhages), the stasis of chyme and gastrosuccorrhoea are likely to be most pronounced. On account of the bleeding and danger from perforation, great caution is advised in the use of the stomach tube. I cannot understand why there should be such danger from the tube under these conditions. Stasis of chyme and gastrosuccorrhoea are the only indications for employing a stomach tube in gastric ulcer, and the muscular spasm caused by these two complications is more likely to cause a perforation than the moderate struggle which accompanies the passage of a tube.

So far as my own experience goes in this matter, I feel quite certain that in several patients with much pain and repeated hemorrhages, the greatest service rendered them consisted in daily lavage of the stomach. Every evening at 9 o'clock from one to two pints of highly acid stomach-contents were removed so the patients were insured a good night's rest. Without lavage the patients had sleepless nights and much pain.

The treatment of hyperchlorhydria and gastrosuccorrhoea is rather disappointing when the ulcer is in an active state. Alkalies before and after meals and belladonna in large doses do not suffice to arrest the symptoms, although in the latent periods the

usual treatment of hyperchlorhydria is much more efficient.

The relation between gastric ulcer and hyperchlorhydria with stasis of chyme is not at all clear. We think of gastric ulcer being the result of two factors, viz., a regional lowering of the cellular resistance, due possibly to a local infection, and hyperchlorhydria.

A problem lacking solution at the present time is the interdependence of hyperchlorhydria, gastric ulcer and stasis of chyme. The causal relation among these three factors has great importance both from the standpoint of pathogenesis and therapy.

If stasis of chyme is responsible for hyperchlorhydria and gastrosuccorhea, then an operative procedure which cures retention of chyme would be a very simple method of arresting a factor which causes most of the trouble the patient suffers, and at the same time a complication would be disposed of which perpetuates the ulcer. An experience in Pawlof's laboratory has a great deal of significance in this relation.

One of the dogs (in which a smaller stomach from the fundus was made), developed an ulcer in the smaller stomach. After the ulcer was formed gastric juice was secreted in three times the amount which was secreted prior to the ulcer formation. In this case spasm of the pylorus, and the presence of food can be eliminated. The only remaining cause which could be responsible for gastrosuccorhea was the presence of the ulcer.

It looks as though an ulcer excites the receptors of certain afferent nerve paths which are responsible for a reflex excitation of the peptic glands. Gastrosuccorhea and high acidity will account of the refusal of the pylorus to allow the passage of chyme into the duodenum.

Admitting this to be the sequence in which these factors originate, we must be reserved in accepting gastro-enterostomy as a clear solution of the whole problem. That gastro-enterostomy does give great relief I readily admit. When retention of chyme is associated with a high degree of acidity, gastro-enterostomy may be followed by complete relief of the stomach symptoms but what followed in two cases in my own experience was a perforating ulcer in the jejunum at the site of operation. Two such experiences have led me to believe that high acidity and an excess of gastric juice in cases of ulcer are the very conditions which demand conservative treatment. I would more readily advise an operation when the acidity is moderate than when it is high.

The third class of cases to which I referred constitute a fair percentage of ulcer cases, and offer great difficulties in differential diagnosis. I mean the patients whom Stiller calls congenital asthenics. These patients are characterized by a floating tenth rib, gastric atony and varying degrees of acidity of chyme. They also give a long history of acid dyspepsia. In such cases the gastric ulcer is merely an incident in the pathological history of the patient and one must not be led into the error of estimating the gastric atony and gastrectasis as the result of an ulcer. The atony and gastrectasis persist in such patients after the ulcer is healed. So does the stasis of chyme persist after healing of the ulcer.

Although I have not seen any such patients operated upon for ulcer, I have seen three operated upon for retention of chyme. In two of the patients the operation gave no relief and in the third the result was very doubtful. Why gastro-enterostomy gives none of the expected relief, I am unable to explain, but the fact was amply proved in two of these patients by the use of the stomach tube, before and after operation. When ulcer does occur in such a patient, great care should be exercised in relieving stasis by the stomach pump and also in treating the hyperchlorhydria by diet and drugs. After these measures have been carefully employed without relief, an operation may be undertaken. The misleading factors in these cases are the atony, gastrectasis and hyperchlorhydria. They may all occur without ulcer and will persist after an ulcer is healed.

The mere fact that a patient has a gastric ulcer with hyperacidity and stasis of chyme are not sufficient to justify an operative procedure. The history of the patient must be carefully considered. If the patient has the stigmata of congenital asthenia and gives a history of dyspepsia existing long before the signs of ulcer developed, then we have not the same expectation of relief from gastro-enterostomy which can be reasonably had in a patient who is free from the stigmata of congenital asthenia and in whom the history indicates that the gastric ulcer and digestive disturbances began at about the same period.

In cases in which ulcer is accompanied by pain, vomiting and stasis of chyme with active peristalsis, few physicians will hesitate to advise an operative procedure, but great care must be taken not to interpret the stasis and hyperacidity and gastrectasis of a congenital asthenic, as being caused by a pyloric ulcer only.

If the pyloric ulcer is not the cause of this train of symptoms, but is merely incidental in the patient's pathological history, then gastro-enterostomy will not afford the relief we may otherwise expect.

During the past few years several celebrated surgeons have sought to invert the old numerical proportion of gastric ulcer to duodenal ulcer, viz., of ten to one. This old proportion has been established by careful observations in enormous numbers of autopsies and clinical experiences, and the pathological and clinical experiences have been consistent. For the peptic ulcer of the stomach and duodenum are sufficiently chronic to leave some traces of their site when healing finally occurs.

The duodenal ulcers, which these surgeons claim to find so frequently, are chloropeptic ulcers as well as the gastric ulcers. We must exercise great caution in adopting these revolutionary conclusions. Their experiences have not contributed anything new to the clinical differentiation between gastric and duodenal ulcer. The interim of comfort after taking food in duodenal ulcer (a point which is so strongly emphasized), was known long before this inversion of the proportion was attempted. The only evidence on which this new proportion is based is obtained by inspection of the peritoneal surface of the duodenum. Now if all these duodenal ulcers have gone so far as to show clear evidences of their position by invasion of the peritoneum they certainly would leave some traces after healing, and both old and recent pathological studies clearly contradict the new proportion these gentlemen propose.

I have had no opportunities to inspect the duodenum of the living when ulcer was present, but I have had some experience in trying to locate the site of ulcers in the intestine during post-mortem examinations on typhoid fever subjects and I know one is often misled in locating an ulcer where none exist, and the observer will often fail to locate an ulcer which is present. Before this new proportion can be adopted we must require much more evidence than has thus far been offered.

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- 702 Rose Bldg.*

Intestinal Hemorrhage in Typhoid Fever.

By JOHN H. LOWMAN.

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The first illuminating evidence of typhoid fever is sometimes an intestinal hemorrhage.

A cook, pursuing her usual avocation, suddenly has a bloody stool; a laundress has, while at her work, an extensive hemorrhage from the bowels. In both instances the illness continues as typhoid fever. In the last autumnal revival of enteric fever I observed three cases of hemorrhage in which the dominant symptoms were those of influenza; sudden onset, chills, general myalgic pains, bronchitis and pulmonary congestion. The hemorrhage came as a sudden pronouncement, for typhoid fever was not known to exist. In one of these instances the Widal reaction was negative two days before the hemorrhage, in the others it had not been sought.

Early intestinal hemorrhage in typhoid is more common than is generally reputed, and in walking cases it is not rare. The usual time of recorded hemorrhages has been during the third week but it occurs often during the second week and occasionally in the first. Thus an intestinal bleeding, even after a few days of fever, must be considered with suspicion and not disregarded as an accidental affair.

It has been impossible to study sufficiently the state of the bowels during the first two weeks of fever, but it can be accepted that sloughing of the necrotic surface and consequent opening of the vessels does not take place until later; hence the early hemorrhages must be explained in some other way. There is first a general hyperemia of the ileum with marked congestion of the patches opposite the attachment of the mesentery. This congestion has been plainly seen during the first few days of the fever when early involvement of the appendix demanded a lap-

arotomy and consequent exposure of the bowel to inspection. In one instance of that character when I was present the congestion of the ileum was marked at what was estimated to be the fifth day of the disease. Then follows the medullary infiltration of the Peyer's patches and solitary follicles, when the inflamed surfaces are thickened and swollen. The tissues are then raised, villous, spongy, friable and frequently infiltrated with blood so that their color is dark red and even black. At this time hemorrhage can and does occur. If the involved patches are numerous the bleeding can be very extensive although it is a capillary and oozing hemorrhage. Early intestinal hemorrhage in typhoid fever does not then result from open vessels or a loosened thrombus but from the congested or hemorrhagically infiltrated lymphatic tissues. Such being the state of the bowels early in the disease, hemorrhage might be anticipated in ambulatory cases, and especially so when a diet regimen had not been carefully followed. Effort, a jar or blow, or marked dietary indiscretion would almost be expected to produce the dreaded accident.

After the infiltration stage which continues well into the second week and even longer, for the evolution of the inflamed patches is successive, there follows the period of anemic necrosis and sloughing when the blood-vessels are easily broken and the bleeding is more frequent and profuse. The hemorrhage continues from non-closure of the vessels, imperfect thrombotic formation and consequent facile reopening of the bleeding channels.

Late hemorrhage even during convalescence, when progressive ulceration has ceased, probably results from reopening of the vessels by expulsion of thrombi, because of the increased vigor of the circulation or even from spontaneous loosening of thrombi, when it partakes of the nature of a secondary hemorrhage.

Late in especially severe cases there is occasionally seen a constant oozing of blood that keeps the stool black for days. The patient grows paler and even develops delirium for the first time, apparently from exhaustion. This is sometimes a renewed capillary hemorrhage and sometimes the result of a veritable hemorrhagic diathesis such as is frequently observed in typhus fever. The hemorrhagic diathesis, fortunately of rare occurrence in typhoid fever, may be extensive enough to cause surface bleeding in many places. I saw one case in which the gums, nose,

stomach and kidneys bled as well as the bowels. In this instance the vessels were so feeble that the perforating arteries of the palate oozed; one could see the blood accumulate at the roof of the mouth and fall in drops upon the tongue.

The hemorrhagic diathesis is the probable cause of some of the extensive intestinal hemorrhages. When the coagulation time is especially slow, and a tendency to bleeding is noticed elsewhere than from the bowels, and ecchymoses are common, the presence of an acquired hemorrhagic diathesis is probable, and its incidence should be seriously considered as the eventuality is a fatal issue.

In 1218 consecutive cases of typhoid fever in Lakeside Hospital there have been 74 cases of intestinal hemorrhage, or 6.07%; 56 of them were men and 18 women. In some years the hemorrhagic cases were more numerous than in others, but this percentage of 6.07, based as it is on a series of cases running over 11 years, doubtless represents the proportionate prevalence of hemorrhage in typhoid fever in this city.

It corresponds closely with reports on this accident elsewhere; thus 4.6%, 4.65%, 5.3%, 6%, 6.3%, 7.3% are figures that are given. In the Johns Hopkins Hospital the figure is 6% while 7% is given in Osler's "System."

Men are more liable to hemorrhage than women but our figures do not represent the exact proportion because the number of men treated was much larger than the number of women, and the proportions have not been accurately calculated. However, it is highly probable that the tendency to hemorrhage is greater in men. There may be other reasons for this than sex alone. The social condition of many of the men is inferior, some are tramps, their physical condition is bad due to alcoholic habits and exposure. Moreover, women are more easily managed; especially, to mention one matter, in the taking of large quantities of water. It is a common belief in the hospital that clinical toxemia is of less frequent occurrence in the women's wards than in the men's. This variant is ascribed to the docility of the women in taking water abundantly.

The Brand system of full baths, modified only as to the temperature, is in common use. All cases are bathed every three hours for 15 minutes day and night in a tub with water ranging from 85° to 95° Fahr., when the temperature of the patient is at 102.5° Fahr.

Although the mortality has been low, the last two years for example less than 2%, some years however being 9%, the incidence of hemorrhage has not been particularly influenced. Certain epidemics in which the expectant treatment has been followed have shown about the same proportion of hemorrhage. Although the water treatment has reduced to 4.15%, the general mortality of 25%, which I showed to be the death rate in Charity Hospital here 25 years ago, it apparently cannot be demonstrated that the tendency to hemorrhage has diminished to any marked degree.

The improvement in the management of typhoid fever has been in the control of the toxemia. In 51 deaths in the wards of the hospital during the past 11 years, 28 were from perforation of the bowels, 11 from hemorrhage and perforation, nine from hemorrhage followed by toxemia, and one from hemorrhage direct. The purely toxic typhoid of a former era is rarely seen today.

The liability to hemorrhage increases with the age of the patient.

In this series hemorrhage occurred:

- Between 1 and 10 years in 1 case.
- Between 11 and 20 years in 16 cases, or 21.6%.
- Between 21 and 30 years in 34 cases, or 45.9%.
- Between 31 and 40 years in 19 cases, or 25.6%.
- Between 41 and 50 years in 3 cases.
- Between 50 and 60 years in 1 case.

This table does not clearly show the proportion because the cases are not classified by ages. There are a much larger number of persons admitted between the ages of 21 and 30 than in any other decade and consequently there would be a larger number of hemorrhages in that period.

Hemorrhage is, however, less likely to occur in childhood; in this series there was but one case. There was but one instance occurring in a patient over 50 years. This is doubtless due to the fact that the intestinal lesions are less prominent in childhood and old age than in adult life.

The incidence of hemorrhage in childhood is ordinarily placed at 1%. In our series of 83 (adding nine to the original series of 74), it would be 1.2%.

The effect of the hemorrhage is greater upon men in early manhood than at other times and greater than the effect upon

women. They grow more ill, more toxic, more delirious and are more apt to die.

Date of hemorrhage: I have already referred to early hemorrhages. They are more frequent than is usually reputed, but in this series they were most frequent between the eleventh and twentieth day, from the time of onset of the disease. They occurred as follows:

Between the first and tenth day, 7 cases, or 9%.

Between the eleventh and twentieth day, 34 cases, or 45.9%.

Between the twenty-first and thirtieth day, 24 cases, or 32%.

On the thirty-sixth day, 1 case.

On the fortieth day, 1 case.

On the forty-second day, 1 case.

Indeterminate, 5 cases.

Those under the tenth day were probably due to hemorrhagic infiltration of the Peyer's patches and were, as a rule, less abundant than those occurring later. One sees sometimes one large early hemorrhage and no more, while after the fifteenth and twentieth days one hemorrhage is apt to be followed by others. They are then presumably due to lifting of the slough, the freeing of the thrombus and the eventual open vessels.

That hemorrhage occurs at the forty-second day of the disease shows that the patient is never free from the danger of bleeding, and since hemorrhages have been reported at the sixth day one sees that the accident is possible at almost any time during the illness.

There were two instances of hemorrhage during the relapse. The illness is usually less severe during the relapse than during the primary attack; the intestinal lesions are less pronounced and the fever less high. Hemorrhage would naturally be a less frequent complication. The fact that hemorrhage occurred but twice in this series bears out the belief that a relapse is apt to be of a milder type than the original attack. Curshman reports but four instances of hemorrhage during the relapse among a large number of cases observed.

It is impossible to determine the amount of blood lost. It is described as small clots, bloody stools, four to ten ounces, or large quantities. Sixteen ounces is not an exaggeration in massive hemorrhages. The number of hemorrhages imputed to a single patient is also subject to suspicion. One hemorrhage may be measured by several stools. The higher the bleeding point the slower the blood passes away from the body. The peristalsis is

notoriously slow in typhoid fever and the blood remains even days in the lumen of the intestine and after death blood is still found there. The clinical symptoms are not always clearly enough defined to fix the hour of the accident and often the visible evidence of the blood is the first evidence, so that when in our records 10 bloody stools are recorded it can not mean of course 10 hemorrhages. Sometimes only a few black clots are seen. Sometimes one, two or three large bloody stools come near together, in which case there has been probably but one hemorrhage. When, however, as in several cases, the hemorrhage continued 7, 8, 9 and 10 days there had probably been several hemorrhages. The smallest hemorrhages must be respected and appropriate precautions taken. In one case a few black clots that were considered of but slight importance were followed in three days by a massive hemorrhage that blanched the face of the patient, lowered his temperature, increased and enfeebled the pulse and threw him temporarily into a state of shock.

The immediate cause of hemorrhage is not ordinarily apparent. It comes suddenly, unexpectedly, like a thunderbolt out of a clear sky, and immediately in massive hemorrhages the clinical picture is alarmingly changed. The flushed face gives way to pallor, the eyes sink into the head, the nose is pinched, the cheeks hollow and mouth compressed, the pulse is weak and rapid, the body is livid and cold and the patient lies apathetically in partial syncope.

In ambulatory cases, as I have said, a cause can be surmised. In those under observation and care an exciting cause is not clear. Bodily activity resultant from delirium, effort, indiscretions of diet, all could be cited, but are more or less speculative. Whether the lifting of the patient to and from the bed into the bath is a cause is open to inquiry. The peripheral vessels are contracted after a cold bath and the viscera are congested, the surface is pale and often cyanotic, the blood-pressure rises though the pulse is usually slower, the patient shivers and complains of cold. These conditions, with the violent movement incident to the lifting of a heavy man, might well be cited as incidental causes. Were the percentage of hemorrhage higher in bathed cases, the above-mentioned influences might well be considered as explanatory of the increase, but as we have shown, the percentage is about the same whether the baths are given or not.

Certain it is, that at the first evidence of intestinal bleeding, though it be never so small, the baths must be stopped and absolute quiet enforced by every endeavor. It would be contrary to good judgment to bathe in a tub a patient who gave even a remote evidence of a recent hemorrhage or the promise of a near one.

The symptomatology of hemorrhage is often indefinite. In this series 36, or 48.64%, gave no prodromata.

The symptoms recorded are:

Foul stools in 1 case.

Diarrhea in 3 cases.

Pain in 9 cases or 12.1%.

Sudden distention in 3 cases.

Fall of temperature in 13 cases, or 17.5%.

Fall in blood-pressure in 1 case.

Delirium in 6 cases.

This list is of value chiefly in stimulating reflection.

Extremely careful observation would modify it. It is my belief that malodorous stools not infrequently precede hemorrhages. Free blood in the bowel is foul and betrays its presence by the escape of fetid gases. Nurses trained in this particular will often prognosticate a coming hemorrhagic stool. With other corroborative symptoms it is by no means as negligible a factor as our series shows.

Diarrhea sometimes precedes bloody stools. When it suddenly follows constipation it should be considered with reference to hemorrhage.

Fall in blood-pressure has not been extensively studied by us but it frequently happens in massive hemorrhage. To make systematic blood-pressure tracings in a very sick typhoid case is, however, a hardship to the patient and a burden to the attendant. In the large proportion of hemorrhages there is no marked change in the pressure. Sudden rise of the pulse with other symptoms is significant, but it must be remembered that the pulse sometimes falls with the blood-pressure and the temperature. This concurrence is by no means unfavorable, on the contrary the slow pulse in hemorrhage has a favorable prognostic value.

In six cases delirium preceded the hemorrhage.

Of interesting moment is the factor pain. In 12.1% of the cases (9) pain preceded hemorrhage, and in two cases this was so marked and so coassociated that it connoted perforation and

impelled to laparotomy for an idea, since there was no perforation. It is well here to anticipate for a moment, long enough to glance at the mortality from hemorrhage and learn that 52.38% of the fatal hemorrhagic cases perforated. With this in mind one can the more readily realize the immense significance of abdominal pain in typhoid fever. It may be due to hemorrhage, to peritonitis, to perforation, to simple hyperesthesia. There are, as well, other causes that find their origin in the glands, spleen, kidneys, bowels, vessels, etc., but one of the first mentioned four factors is the highly probable cause of abdominal pain in typhoid fever. With diarrhea pain is more frequent and misleading. The abdomen is tender, but it is generally tender. The pain in hemorrhage is more localized and persistent. The physician sometimes fancies when he suspects a hemorrhage that he can detect a boggiess in the intestinal convolutions as if they contained a thick grumous fluid. One would not expect rigidity but the heightened nervous perception of some individuals causes a fixity of the abdomen that is very disturbing to the observer. Hyperesthesia will do the same thing but here the fixity partakes more of the character of a sharp reflex. Some typhoid cases pursue their entire course with a rigidity of the anterior abdominal wall that precludes any deduction and is a continuous source of anxiety to the attendant. This pain caused by hemorrhage will, at times, be associated with a rigidity that defies analysis.

I may be pardoned here for trespassing beyond the tenor of this resumé by the citation of an instance where the patient came to a useless operation because of hemorrhage. She had had moderately abundant, bright red, bloody stools which were apparently due to one hemorrhage and did not seriously change her condition. Of a morning she had severe pain in the left upper quadrant of the abdomen. There was definite pain to the finger point and, possibly, slight rigidity, yet the abdomen moved synchronously with the respiration. It was surmised that the bleeding point might be in the colon and the floor of the ulcer on the serous coat. The following night there was again a moderately abundant red stool followed by considerable depression of the vitality of the patient. In the morning the pain had increased and was distinctly localized. Abdominal breathing was circumscribed but all respiratory movements were weak and

shallow. As the day dragged on the pain increased, the abdomen became more fixed and rigid. Laparotomy was done, no perforation was found and the cultures taken from the abdominal cavity were sterile.

Opium is often used in hemorrhage. In view of the fact that the question of perforation may arise the use of this drug might prevent a diagnosis. I have in mind one case of hemorrhage in which opium was used to excess and the symptoms of perforation were obscured so that the opening was not even suspected and was found only at autopsy.

In 17.6% of the cases of hemorrhage there was a fall in the temperature. These were all more or less severe but the observation was not always made before the visible signs of bleeding. The fall was from two to five degrees. In few instances it went below the normal point. Ordinarily it returned to the previous high grade in six to twelve hours. A persistent low temperature after hemorrhage is prognostically unfavorable and bespeaks low resistance. A rapid return of the fever shows vigorous power of reaction and a more decided and persistent strength. In one case a severe hemorrhage in the latter part of the third week was associated with a decided drop of the fever and a persistent low temperature while the patient gradually and rapidly went on into convalescence. Such instances may possibly have been formerly more common and may have lead Trousseau and his school to the belief that hemorrhage had a beneficent potentiality, a most erroneous position which only an occasional and exceptional instance could have suggested. Sudden pallor, pulse acceleration, restlessness with an abrupt critical drop in the temperature are the marked prodromic symptoms.

Of those attacked with intestinal hemorrhage 20 to 30% die. Of the hemorrhage cases in this series 21 individuals, or 28.37% died; this is 1.72% of the entire number of cases. Of the 21 cases 11, or 52.38%, died of perforation, representing 14.8% of the hemorrhagic cases. Nine, or 12.16%, died of toxemia and one from the immediate direct effects of hemorrhage.

I have already hinted at the high percentage of perforations in hemorrhage cases. I apprehend that the idea of perforation is not ordinarily associated with that of hemorrhage. When these two accidents, the most serious that can complicate the course of typhoid fever, coexist in the same individual death is almost absolutely certain.

The time of perforation after hemorrhage was noted in eight of the eleven cases and was:

- 1 day after hemorrhage in 1 case.
- 2 days after hemorrhage in 1 case.
- 3 days after hemorrhage in 1 case.
- 4 days after hemorrhage in 2 cases.
- 5 days after hemorrhage in 1 case.
- 4 weeks after hemorrhage in 2 cases.

Thus in six instances it is presumable that the hemorrhage and perforation were incident to the same lesion although naturally this is not absolutely certain.

Of all (39) perforations 28.02% were preceded by hemorrhage. The association of perforation and hemorrhage which a study of this series shows is a most interesting demonstration.

Operation for hemorrhage is of doubtful utility. It is difficult, if not impossible, to find the bleeding points, the dark places that look threatening are due to hemorrhagic infiltration and are not especially dangerous, certainly not dangerous enough to require interference; the manipulation of the bowels necessary to find the bleeding ulcers is of itself provocative of renewed bleeding.

In anticipation of the perforation which intervenes in 52% of the cases of hemorrhage it is very desirable to localize the bleeding point as a guide of more or less importance to the surgeon. It does not follow, of course, that the bleeding ulcer is the one that perforates. Much depends on the rapidity of the operator and everything possible should be done to aid his celerity and despatch. *Cito, tuto et jucundo* should be his motto with emphasis on the first part of this old legend. I fancy that the surgeons of the old French school that flourished before the days of anesthesia would have surpassed in results the careful dissecting surgeons of our day.

When the classical picture of hemorrhage presents itself and a red bloody stool follows sharply on this dreaded apparition, the bleeding originates in the neighborhood of the cecum. Perhaps above, perhaps below, but somewhere thereabout. If the hemorrhage comes on tardily and is black and tarry its origin is high in the ileum and possibly in the jejunum. When the usual symptoms are associated with vomiting the hemorrhage is likely to be high in the small intestine. The behavior of the stools in conjunction with pain will give a reasonable idea of the position of the dangerous ulcer.

However in our series pain was present in only 12.1% of the cases and fall in temperature in but 17.5%, so that there could be no guide in about three-fourths of the cases except what was gained from the stools alone.

The chief therapeutic conception in intestinal hemorrhage is the securing and maintenance of an empty and collapsed bowel whereby the vessels will be compressed and the conditions favoring arrest of hemorrhage will obtain. As in bleeding ulcer of the stomach so long as the viscus is distended the openings of the broken vessels more easily remain patulous. If the stomach or the gut can be emptied and the sides of the organ made to fall together the bleeding points are compressed and the hemorrhage mechanically stopped. Other remedial agencies such as cold, astringents, the arousing of vasomotor forces, opium or operative means are insignificant in comparison, valuable as they may be as secondary aids. Fortunately the increased volume of the intestinal contents provokes a large stool and the bowels are partially emptied. The use of a hydrogogue cathartic is thus not necessary. It is moreover questionable whether a purgative should be used in any but early hemorrhage. In the stage of medullary infiltration it could be considered with the expectation that it would act favorably on the swollen tissues as well as empty the bowel. On the other hand early capillary hemorrhages, though sometimes abundant, are very rarely continuous and a cathartic is not demanded. In late hemorrhages with ruptured blood-vessels, the increased peristalsis would be only too apt to increase the hemorrhage. Some of the contents must therefore be left; the bowel can not safely be absolutely cleaned. All food must be interdicted; nothing, not even milk, should be allowed; water can be permitted. As patients very very rarely die as the result of the hemorrhage, and then almost always after several, as shown by one death in this entire series, one can reasonably expect that the patient will quickly recover from the results of his acute anemia, and the entire energy of the physician can be devoted, for a time at least, to stopping the bleeding. The abstinence can be continued six days after the hemorrhage ceases. This plan of complete abstinence has been pursued with especial vigor during the past two years and is probably responsible for the reduced mortality during that time. A Leiter coil or cold applications to the abdomen, stimulants hypodermically, opium

in small quantities for restlessness and active peristalsis and water are incidentally used as required; all bathing except for comfort is stopped. This should be done on the slightest suggestion of danger even though extreme measures are not considered necessary. Lactate or chlorid of calcium is employed almost as a routine although its use is not scientifically demanded unless the coagulation time is slow which is not always the case. It is tedious and rarely practicable to estimate the coagulation time, one therefore takes the chance of benefit from it. The older remedies, turpentine and ergot, are useless. Opium abolishes peristalsis and is an effective aid. Absolute quiet is essential. In one case, however, in which the hemorrhage was alarmingly extensive and repeated, a large bed-sore developed from the complete rest which was earnestly enjoined.

In nine cases marked toxemia developed with delirium, restlessness, dry tongue, high fever and exhaustion and caused a fatal issue. The withdrawal of the water and the baths, the chief enemies of toxemia in typhoid fever, were largely responsible for this development. The anemia, exhaustion, enfeebled cardiovascular energy, and the cerebral ischemia, by lessening all the protective agencies of the body, contribute to the toxemia as well. Drugs prevail but feebly against it, yet one uses the usual group of strychnin, caffeine, alcohol, digitalis and camphor in a vain hope. But it seems sometimes like beating against a stone wall. Hypodermoclysis, oxygen, all the agencies in fact that are known to prevail against profound exhaustion should of course be used.

The supreme consideration to have in mind is the necessity of placing the bowel in a state of absolute rest and collapse.

Hemorrhage is the serious accident of typhoid fever. It causes more deaths than any other complication. Its advent is the instant of alarm. With its coming the patient loses at once twenty to thirty chances out of a hundred for his life. Small wonder then that its clinical history should arouse so active an interest.

1807 Prospect Ave.

Reprinted from the MEDICAL RECORD, February 20, 1909.

A CASE OF ACROMEGALY WITH THROMBOPHLEBITIS OF THE SUPERFICIAL VEINS.

A STUDY OF THE CARDIOVASCULAR CHANGES IN
ACROMEGALY.

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THIS case of acromelagy is considered worthy of report because of the occurrence of thrombophlebitis of the superficial veins. In a careful search through the literature I have been unable to find a similar case recorded.

R. W., male, aged 51, Lakeside Hospital Medical No. 5685, was admitted to Lakeside Hospital May 28, 1906, on the service of Dr. E. F. Cushing, to whom I am indebted for the privilege of making this report. The patient complained of stomach trouble, swelling of the feet, and shortness of breath on exertion. The family history threw no light on the case. He had typhoid fever when eleven years of age, and rheumatism in the spring of 1905. Following his attack of rheumatism he had shortness of breath, weakness, and swelling of the feet, which persisted with some intermissions until his admission to the hospital. He had always used whiskey, beer, tea, coffee, and tobacco very freely. He had gonorrhea eighteen years previously, but had never had

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syphilis. On inquiry as to whether his hands and feet had become larger or his voice coarser in recent years, he thought that they had, though he was of such a low grade of intelligence that he paid little attention to these details. However, his sister,



FIG. 1.—Showing the appearance of the patient when 28 years old.

who came to visit him at the hospital and who had not seen him for ten years, said that he had changed so that she could scarcely believe he was her brother. She said his hands were very much larger, that he wore much larger shoes, and his voice was much coarser than when she had last seen him.



FIG. 2.—Showing the appearance of the patient at the time of admission to hospital.

The illness for which he was admitted to the hospital began one year before with weakness and shortness of breath on exertion. He also had marked swelling of his feet. This condition con-

tinued with intervals of improvement until he was admitted to the hospital. At that time he had severe attacks of nocturnal dyspnea.

Physical Examination.—Patient was a large, heavily built man, height 5 feet 8 inches, weight 210 pounds. He stood with his feet quite wide apart, and his shoulders and head bent forward so that he looked from under his eyebrows. He answered questions readily, but his mentality was below normal. His face was massive, deeply wrinkled, especially about the forehead, his expression sorrowful, though he was quite good natured. His general musculature was quite well developed, but not in proportion to his massive size. The skin of his face was dark from exposure, and felt thick. His hair was very coarse, had a tendency to stand up, and the hair line came down low on his forehead. His head was round in shape; the external occipital protuberance stood out as a rounded prominence, the base of which was 3 c.m. in diameter and raised 2 c.m. above the surface. The superior curved lines of the occipital bone formed very prominent ridges. The glabellæ of the frontal bone were very prominent, owing no doubt to the enlarged frontal sinuses. The superciliary ridges of the frontal bone were much enlarged. The zygomatic arches were massive; the malar bones and the infraorbital portions of the superior maxilla stood out as large prominences due probably to the enlarged cavity of the antrum. The nose was large and globular and the alæ were very thick; the hypertrophy affected chiefly the cartilages and soft parts of the nose. His mouth was large, the upper lip 1.5 c.m. thick, and the distance from the lower border of the nasal septum to the margin of the upper lip was 2.5 c.m. The lower jaw was large and projected forward so that in closing his mouth the lower teeth were in

front of the upper. The teeth showed considerable decay and those in the lower jaw showed distinct spacing. The alveolar processes were 2.5 c.m. in width. The palate arch was very high, extending upward as a deep groove 2.5 c.m. wide and 1.5 c.m. deep, the deepest part being posteriorly. The tongue was dry, not coated, very large, with deep fissures on the dorsum, and the papillæ were very much hypertrophied. The tonsils were slightly enlarged, the epiglottis smaller than normal, and the vocal cords moved freely but were considerably thickened.

His speech was slow and the tone of his voice harsh and deep. His hearing was good; the lobules of his ears were very large. The circumference of his head measured 58 c.m., from the point of his chin to the hair line on his forehead 21 c.m. The examination of the eyes revealed nothing abnormal except the limitation of the visual fields (see diagrams).

His neck was large and very short. The thyroid cartilage was massive and the pomum Adami was very prominent and sharp. The thyroid gland was palpable but not enlarged. There was no general glandular enlargement.

The chest was barrel-shaped with a very marked cervicodorsal curve. The spinous processes of all the vertebræ were prominent and thickened, especially the spines of the seventh cervical and first dorsal vertebræ. The spinous processes of all the dorsal vertebræ were much lengthened. The shoulder girdle was massive.

The clavicle was long and broad, its curves accentuated, and much roughened at the site of the attachment of the muscles. The scapula was very broad and the spine, the acromion, and the coracoid process were rough, thickened, and enlarged. The

costal angle was very obtuse. A broad shallow funnel-shaped depression was noticed over the lower part of the sternum. The manubrium sterni was broad and formed a sharp angle with the gladiolus. The percussion note over the upper part of the sternum was quite dull. On the left side at the costal

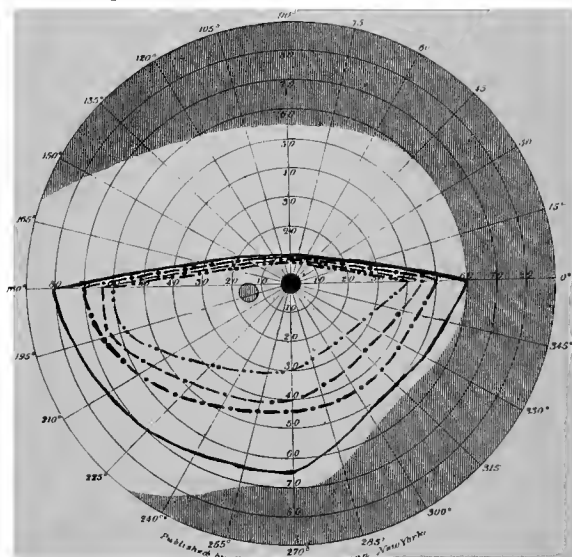


FIG. 3.—Fields of Vision in the Left Eye. Form outline, —; blue, . — . —; red, . — . — . —; green, —

margin in the mammary line a distinct bone deformity, the result of an old injury, projected 2.5 c.m. above the surface. The circumference of the chest was 101.5 c.m., expansion 1.5 c.m. His lungs were clear throughout to percussion and auscultation.

The point of maximum impulse of the heart was feeble, somewhat diffusely seen and felt in the fifth

interspace just outside of the mammary line. The relative cardiac dullness extended to the left 14 c.m. from the midsternal line at the level of the fourth rib, and to the right 2 c.m. beyond the right sternal border at the same level. The first sound of the heart was very irregular both in force and

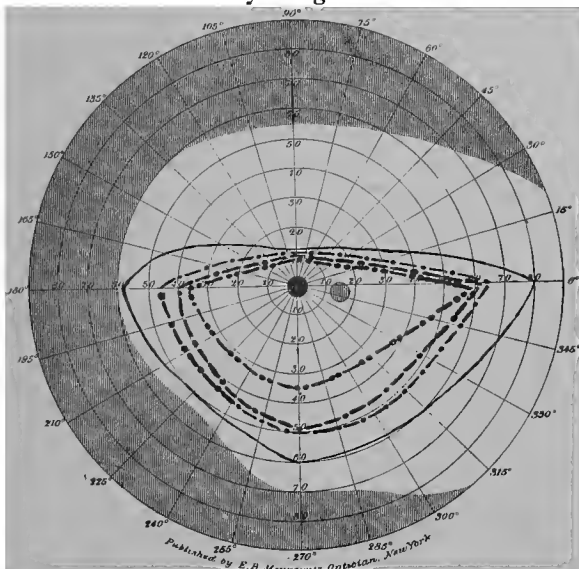


FIG. 4.—Fields of Vision in the Right Eye. Form outline, —; blue, . — . —; red, . — . —; green, . . — . —

rhythm, and at the apex could be heard a soft blowing systolic murmur, which was transmitted faintly into the axilla, but could not be heard in the back. The second sound in the aortic area was considerably accentuated. His pulse was irregular and arrhythmic, volume full, pulse rate, 66. The arteries accessible to palpation were all large and showed

considerable sclerosis. The blood pressure was 170 mm. (Riva-Rocci instrument, Cook's modification, 10 c.m. band.)

The abdomen was quite pendulous. The growth of hair over its lower part was abundant but not unusually so. The spleen was not palpable. The lower border of the liver could be felt 3 c.m. below the costal border. There was no abdominal tenderness and no masses were felt. His penis and testicles were normal in size.

His hands were very large and spade-like in character, the increase in size being more marked in breadth than in length. The thenar and hypothenar eminences were very prominent and heavily padded. The skin of the palm threw itself into thick folds when the hand was closed, similarly when the fingers were extended thick folds appeared on the dorsum of the hand. The thumb was short, stood away from the index finger, and the dorso-palmar diameter was very long because of the thick padding of the ungual phalanx. The distal phalanges of the fingers were very thick, due to the similar padding of the palmar surface. The fingernails were large, shiny, and markedly curved, and showed numerous linear striations. The fingers had a tendency to stand apart as though they were prevented from lying close together by the large size of the metacarpophalangeal joints. When the wrist was tightly compressed a distinct flush of the hand unaccompanied by pain soon appeared, the veins being full and the arteries throbbing. This flushing was similar to that seen by the writer in a case of erythromelalgia in the same ward a few months before. The circumference of the palm of the hand was 25 c.m., of the wrist 18.5 c.m.; the length of the middle finger was 9 c.m., its greatest circumference 8 c.m. The musculature of the forearm seemed

rather scanty when compared with the unusual size of the hand.

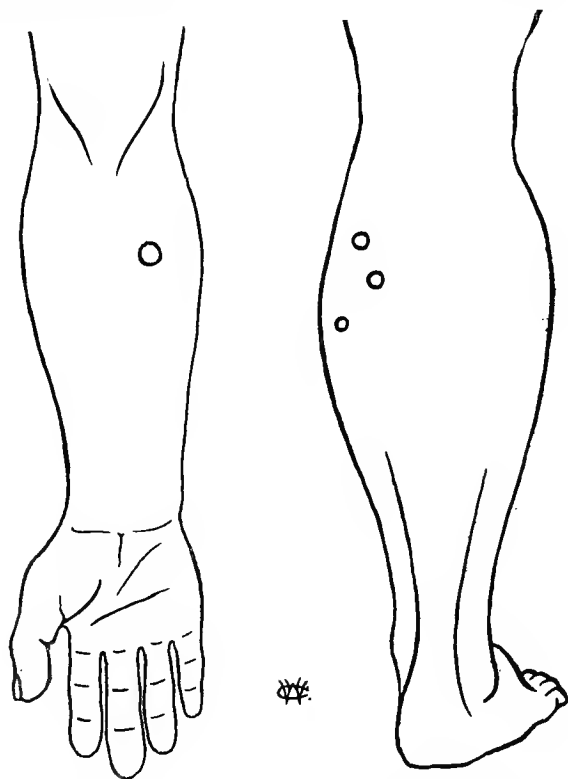


FIG. 5.—Showing the points of induration due to thrombophlebitis.

The feet showed changes similar to those described in the hands. They were very large so that he had to have his shoes made to order. The increase in size was chiefly in the breadth, the toes

being short and thick with heavy padding on the plantar surface. The great toe was extremely large. The nails showed marked trophic changes, being thick and markedly curved. When the feet were allowed to hang down with the patient sitting on the side of the bed, they rapidly showed a flushing brighter even than that described in the hands, with a similar dilatation of the veins and throbbing of the arteries. His patellar and Achilles tendon reflexes were present but sluggish. There was no disturbance in any part of the body of the sensation of touch, pain, heat, or cold. There was some edema of his shins.

His urine was scanty, highly colored, specific gravity 1024, reaction acid, albumin heavy trace, no sugar; microscopic examination showed an occasional leucocyte and epithelial cell, a few hyaline and granular casts.

The examination of the blood gave the following count: Red blood corpuscles 4,958,000, white blood corpuscles 6,800, hemoglobin (Dare) 80 per cent. The differential count of 500 leucocytes showed polymorphonuclears 51.5 per cent., small mononuclears 43.5 per cent., large mononuclears, 4.7 per cent., eosinophiles, 0.3 per cent. The red corpuscles stained well and were normal in size and shape.

With rest in bed and appropriate treatment his cardiac compensation was soon restored and his dyspnea and edema disappeared. During his entire stay in the hospital his skin was always bathed in perspiration.

The unusual feature of this case was the appearance in the middle of each forearm, eighteen days after his admission to the hospital, of small symmetrically-situated indurations. These were quite tender, 2 by 3 c.m. in size, and it could easily be determined that they were due to thrombophlebitis of

the superficial veins. They soon lost their tenderness and disappeared in about ten days, leaving only a slight thickening. A few days later similar tender indurated areas appeared in each calf about midway between the knee and ankle joint. These also were definitely associated with the superficial veins. In all there were eight of these indurations due to thrombophlebitis. They were unassociated with rise of temperature or leucocytosis.

The patient died very suddenly a few days after leaving the hospital, and unfortunately an autopsy was not obtained.

Little attention has been paid by writers on the subject of acromegaly to the cardiovascular changes of this disease. In many cases hypertrophy and dilatation of the heart associated with arteriosclerosis have been described, but without comment, the writer apparently regarding the condition as a mere coincidence. Marie¹ mentioned the fact that syncope was a common cause of death in these patients and that they frequently had varicose veins.

Huchard² was really the first to call attention to the cardiovascular changes in acromegaly. He described three cases. In the first there were marked symptoms of angina pectoris. The second, a man 57 years old, seen fifteen years after the first signs of acromegaly developed, had cardiac hypertrophy with arrhythmia. The third case, a man 62 years of age, had all the signs of sclerosis of the heart with pronounced increase in the cardiac dullness, dilatation of the heart, and interstitial nephritis. Later his patient had breaking down of compensation, edema of the legs, and pulmonary infarction. J. B. C. Fournier³ in 1896 in a thesis reviewed the literature of acromegaly up to that date and found twenty-five cases in which there were cardiovascular changes. Of the cases quoted by him the heart

was enlarged in all except in the case described by Henrot. In this patient a man aged 35, the heart was small, the walls thin and flabby, but without any degeneration of the heart muscle. In Dallemagne's⁴ case, quoted by Fournier, a man aged 47, who died from diabetic coma, the heart at autopsy weighed 885 grams. The wall of the left ventricle was 3 c.m. thick; the valves were not diseased except that the free edges of the mitral valve were slightly adherent. Histological examination showed an hypertrophy of the muscle fibers to double their normal size and a slight effacement of their striations, but without sclerosis or granular degeneration. The vessels showed thickening with yellow plaques of sclerosis and obliteration of the small branches of the arteries (endarteritis and periarteritis). In a second case recorded by Dallemagne the heart weighed 830 grams. Fournier divided the cardiac changes into two classes: (1) A simple enlargement of the heart (cardiomegaly) without degeneration of the muscular fiber, the heart participating in the increase in size of the other organs (splanchnomegaly); (2) an hypertrophy in which there is a true sclerotic myocarditis, a cardiorenal arteriosclerosis often with enlarged liver, edema of the feet, albumin in the urine, and not infrequently angina pectoris. He attributed the arrhythmia to the direct action of the poison of acromegaly on the muscular fibers of the heart.

Klebs⁵ attached a great deal of importance to the changes in the vessels. He found a great increase in the caliber of the vessels with thickening in the internal and external coats. In his patient, a man 40 years of age, the heart at autopsy weighed 550 grams; the mitral and tricuspid valves were insufficient. The vessels participated in this hypertrophy and dilatation.

The following are the measurements of the vessels, the figures noting the circumference of the vessels in millimeters: pulmonary artery outside the valves, 90; aorta outside the valves, 85; ascending aorta, 77; thoracic aorta under left clavicle, 60; intercostal arteries, 56; renal arteries, 36; lumbar arteries, 41; right iliac artery, 28; left iliac artery, 28; hypogastric artery, 18; external iliac artery, 24; femoral artery at Poupart's ligament, 20; deep femoral artery, 20; right subclavian, 34; right common carotid, 23; left common carotid, 23; right internal carotid, 26; right external carotid, 26; right vertebral artery, 14; thyroid artery, 10.

Tikomoroff⁶ considered that the vascular lesions presented three stages, viz., (1) dilatation of the vessels, (2) thickening of their walls, (3) obliteration of their lumen. In some cases the vessels were transformed into fibrous cords. The thickening affected the media chiefly. In the various organs the walls of the vessels were thickened and dilated, sometimes causing hemorrhages through rupture. Furnival⁷ reports a case of a man, age 58, with the usual signs of acromegaly. He was killed by a train and at autopsy the heart was found hypertrophied but no changes were noted in the valves. The kidneys showed an interstitial fibrosis. In discussing the pathological anatomy, the data for which was largely obtained from Sternberg's⁸ Monograph, he says that the arteries are thickened and dilated, all the coats being affected by fibrosis, but especially the intima. These changes begin in the aorta and pulmonary artery and spread to the smaller vessels. The dilatation is probably secondary to the degeneration of the vessel walls, although Klebs maintained the contrary. The heart is generally hypertrophied and dilated, which is probably due to the changes in the blood-vessels. The kidneys

are usually large and show signs of a chronic nephritis, the changes in the kidney being secondary to the cardiovascular lesions. In Hunter's⁹ case, a male, 52 years of age, the heart weighed 26 ounces, showed general hypertrophy and dilatation, and the arteries at the base of the brain were very atheromatous. Claude and Moxter have also found marked arteriosclerosis.

At a meeting of the Association of American Physicians in 1897, O. T. Osborne¹⁰ reported the clinical history and the autopsy findings in a patient who died at the age of 47 years from syncope. The heart was enormous, being 15 inches in circumference at the base of the ventricles and weighing two pounds and nine ounces. The wall of the right ventricle was three-eighths inch thick, that of the left seven-eighths inch. The valves of the heart were normal except for some slight thickening at the edges of the aortic valve. The coronary arteries were enlarged, admitting an ordinary lead pencil into their orifices. No occlusion of the heart vessels was found. In Leszynsky's¹¹ patient the heart was not enlarged and the arterial tension was normal, but four months later his heart action became feeble, albumin and casts appeared in the urine, and he developed a left-sided hemiplegia which was fatal. Labadie, Lagrave, and Deguy¹² have reported two cases with marked hypertrophy of the heart and arteriosclerosis. In one the heart weighed 1240 grams, and the radial artery was so sclerosed that it felt like a goose quill. Levi,¹³ in a general review, gives among the symptoms of acromegaly, hypertrophy of the heart, arterial hypertension, and varicose veins. He summarizes the relation between this disease and the cardiovascular lesions as follows: The heart is hypertrophied, the aorta and pulmonary artery are the seat of thickening and

dilatation; these alterations reach the ramifications of these trunks; as a result of a dilatation of the heart, the viscera show the evidences of a stasis. Mitchell and LeCount,¹⁴ in reporting the autopsy findings in a patient with acromegaly, whose heart weighed 450 grams and whose vessels were quite atheromatous, made an extensive review of the literature and found only eight cases, in which the condition of the heart was noted, in which enlargement was not found. Of these Hanseemann found brown atrophy; Roxburgh and Coltes normal; Dallemagne atrophied (the same author reported two cases where the heart weighed 885 and 830 grams respectively); Henrot a curious atrophy of the heart and blood-vessels; Boltz, Frankel, slightly atrophied; Johnstone and Monroe, 225 grams.

The veins show changes similar to those described in the arteries. Varicose veins of the lower extremities are seen in nearly every case. It is easy then to understand the occurrence of thrombophlebitis as seen in the case here reported.

Whether the cardiovascular changes are a mere coincidence or one of the clinical features of acromegaly is the question to be decided. If the hypertrophy of the heart and the arteriosclerosis are due to the same cause as the changes in the bones, what is that cause? It is the opinion of the writer, both from a study of the clinical features of acromegaly and from the present physiological knowledge of the effects of extracts of the pituitary gland when injected into the circulation, that the cardiovascular changes should be considered as much a part of the clinical picture of acromegaly as the changes in the bones, and should be so recorded in our text books. The condition of erythromelalgia, which has been noted in acromegaly by several writers and

was present in mild form in my case, is corroborative of this opinion, as Weir, Mitchell, and Spiller have shown that this condition depends upon an obliterative endarteritis of the vessels of the extremities.

In 1895 Oliver and Schäfer¹⁵ found that injections of extracts of the pituitary caused usually a marked rise in blood pressure associated with an augmentation of the force of the heart beat. Szymonowicz¹⁶ in 1896 in two experiments upon dogs obtained a slight fall of blood pressure and a quickening of the heart beat. In 1898 Howell¹⁷ tested separately extracts of the anterior lobe and of the posterior lobe of the pituitary of the sheep by injection into the circulation of anesthetized dogs. He found that extracts of the anterior lobe produced little or no perceptible change in blood pressure or heart rate. Extracts of the posterior lobe, however, in a dog with vagi intact, produced a pronounced slowing of the heart beat, together with an increase of blood pressure; while in a dog, with the vagi cut or under the influence of atropine, a prolonged rise in blood pressure was produced together with a stronger and slower heart beat. Magnus and Schäfer¹⁸ in 1901 found that intravenous injection of saline extract of the posterior lobe is followed by a marked increase in the flow of urine. Schäfer and Herring¹⁹ confirmed this observation and showed the striking parallelism which exists between the pituitary and the suprarenal bodies in development, structure, and functions. In each gland there are two parts, one of which, a highly vascular epithelium, yields an extract which is inactive; the other, of neuroectodermic origin, yields an extract which has a pronounced effect upon the heart and arteries. They advance the supposition that the epithelial part of each organ furnishes a secre-

tion which passes through certain stages of formation, and that its production is merely completed by the neuroectodermic part, where the full activity of the secretion is acquired. Herring claims that there is histological evidence of the passage of this secretion into the third ventricle to mix with the cerebrospinal fluid. He claims that it is difficult to conceive that the posterior lobe of the pituitary should furnish an active secretion according to the usual views held of its structure. Cramer²⁰ has shown that strong extracts of the pituitary body produce within one or two hours a distinct dilatation of the pupil of the enucleated frogs' eye, but visible only after twelve or more hours with dilute extracts. The action of a solution of adrenalin on the pupil is more rapid but not so lasting.

Various theories have been advanced as to the essential cause of acromegaly. The majority of observers believe that the disease is associated with some alteration in the function of the pituitary body of which Rolleston²¹ suggests three forms of modifications, viz., (1) suppression, a condition of incompetency of the pituitary analogous to myxedema or Addison's disease. Such incompetency would imply either an atrophy of the pituitary gland, which is not in accordance with the post-mortem findings, the reverse being the case, or else destruction by tumor; (2) hypersecretion, due to the excessive activity; this view is born out of observations of simple hypertrophy of the hypophysis. The administration of pituitary extract would be expected to aggravate the symptoms. However, I think that the action of the pituitary extract like that of the parathyroids can not always be depended upon, as its active principle may be destroyed in the preparation. (3) Perverted function due to heter-

ogenous transformation of the structure of the pituitary body.

The pathological changes in the gland point quite strongly to the hypersecretion theory. Hypertrophy of the prehypophysis with increased vascularity and increase of the chromophile cells, or adenomata are the most frequent lesions. Brooks²² found the latter condition at autopsy in his three cases. Atrophy of the gland has never been reported except in the single instance of Mossé and Daunic,²³ and only very exceptionally has it been stated as normal in size. Many observers have found sarcomata of the gland, but, as Brooks points out, these were probably adenomata, as it is difficult to distinguish the two conditions. In fact in his first case he diagnosed the condition of the pituitary as a sarcoma, until with further study and comparison with his other cases of the disease, he came to the conclusion that the growth was an adenoma. Further the long course of the disease, in many cases twenty or twenty-five years is not consistent with sarcoma, nor have metastases been described in any of the cases. The increased secretion of the prehypophysis in acromegaly is claimed by Brooks to act as a stimulus to the overgrowth of the connective tissue cells leading to changes in the vessels, overgrowth of bones, and enlargement of the viscera.

The condition of arteriosclerosis with hypertrophy of the heart can be explained on the theory of hypersecretion of the pituitary. As stated above the action of extracts of the posterior lobe of the pituitary on blood pressure is analogous to that of extracts of the suprarenal gland. Josué, Erb, Fischer, Klotz, and others, have shown that arteriosclerosis of the aorta extending even to the peripheral vessels can be produced in rabbits by injections of adrenalin. If the supposition of Herring is correct

that the anterior or epithelial portion of the pituitary body furnishes the secretion, the production of which is merely completed by the posterior part, where its full activity is acquired, then hyperplasia or adenomata of the anterior lobe, such as is found in acromegaly, would increase the secretion to be activated by the posterior lobe and passed on into the third ventricle. The increased secretion would cause a continued rise in blood-pressure which would eventually produce arteriosclerosis with subsequent hypertrophy of the heart.

General Conclusions.—Enlargement of the heart, either simple or associated with a myocarditis, is the condition usually found in acromegaly. Sclerosis of the arteries and degenerative lesions affecting the walls of the veins, with dilatation and subsequent obliteration of their lumen, are constantly present. These changes in the heart and vessels should be considered as much a part of the clinical picture as the changes in the bones, and they are probably due to the prolonged hypertension of the vessels, the result of hypersecretion of the pituitary body.

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Perineal Herpes in a Case of Pneumonia in a Child Eight Months Old.

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Perineal herpes developing during the course of pneumonia is a very unusual condition. Among recent writers Osler¹ and Musser² mention that it may occur. Samuel West³ quotes one case from the literature in which an herpetic eruption appeared about the anus during the course of a pneumonia. The actual percentage showing labial herpes, as given by different authors, varies from 14 to 43. Howard⁴ thinks that the most reasonable explanation of the frequency of the nasal and labial herpes, is due to the marked passive congestion, which is so often present, affecting the Gasserian ganglion and was especially noticeable in one of the cases he reported. The same writer reports one case of pneumonia in which herpes was present in the mid-dorsal region on the left side, extending from the middle of the back to about the anterior axillary line, corresponding to Head's sixth dorsal area. Two days before death a similar eruption appeared in the left umbilical and iliac regions (eleventh dorsal area). Microscopic examination of the posterior root ganglion of the eleventh dorsal nerve showed hemorrhage, infiltration of round cells, and degeneration of the ganglion cells. No lesions were demonstrated in the posterior nerve roots, in the spinal cord or

Read before the Ohio State Medical Association, Cincinnati, May 5, 1909.

in the peripheral nerves. He also found similar changes in the Gasserian ganglion in a patient dying on the sixth day of acute lobar pneumonia in whom there was a marked nasal and labial herpetic eruption. Cases have been described in which the herpes have developed upon the arm, the back, upon the cornea and upon the sternum. Wilson Fox, quoted by West, has observed a similar rash upon the tongue, soft palate and tonsils. It usually appears from the second to the fifth day, though it may be delayed until after the crisis. Because of the infrequency of perineal herpes the following case is considered worthy of report:

Ruth E., aged eight months, was admitted to Lakeside Hospital on the medical service of Dr Henry S. Upson, September 30, 1906, with a history of cough and fever. Her maternal grandmother had died of pulmonary tuberculosis. The baby had always been quite healthy with the exception of a cold in the head with some cough at intervals during the past four months, which was evidently due to the presence of adenoids.

Present Illness. For the past three days the child has had fever and cough and has been breathing rapidly. She has refused her nourishment and has had some vomiting. The bowel movements have been normal. There has been considerable loss in weight.

Physical Examination on admission showed the child to be quite well nourished and she did not appear to be extremely ill. The respirations were 60 to the minute and there was very active dilatation of the alae nasi. There was some suppressed cough and the expiration was accompanied by a grunt. A slight mucopurulent discharge from both eyes was noticeable. The ears, nose and throat were normal. The chest was well formed but a slight rosary could be felt. There was slight diminution in expansion over the upper part of the right side of the chest. Over this part the tactile fremitus was increased. On percussion there was marked diminution in resonance over the front and back of the upper part of the right side of the chest and here the breath sounds were bronchial in character, and towards the end of inspiration a few fine crepitant rales could be heard. The remainder of the right and the entire left lung were clear throughout to percussion and auscultation. The heart was normal in size and the sounds clear, but there was quite marked accentuation of the second sound in the pulmonic area.

The abdomen was normal. There was no edema of the shins and the reflexes were normal. The leukocytes numbered 22,300.

The child was given the usual treatment of abundance of fresh air, and stimulation with strychnin and whiskey when indicated. The temperature began to fall by lysis after the seventh day of the disease. The temperature varied from 102° to 103.5° and at times the child was quite cyanotic. The urine showed a slight febrile albuminuria.

On the third day after admission a marked herpetic eruption appeared upon the perineum to the left of the median line, extending forwards to the posterior part of the labia majora and partially encircling the anus (Fig. 1). Two days later the vesicles were mostly replaced by

yellowish crusts. In the course of a week the crusts had nearly all disappeared, leaving an area covered with dusky red papules. According to Cushing the area affected would correspond to a lesion of the posterior root ganglion of the fourth, possibly fourth and fifth, sacral nerves. The child made a very good recovery.

It was not until 1861 when the classical paper of Von Barenprung⁵ first appeared that herpes zoster was considered to be definitely of nervous origin, and from the results of post-mortem examination he located the lesion in the posterior root ganglion. Until the publication of the admirable paper of Head and Campbell⁶ in 1900 there were only two well reported autopsies

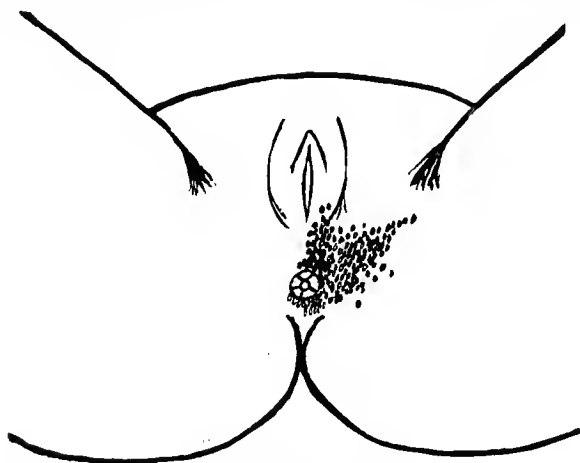


Fig. 1.

on cases of herpes zoster in the trigeminal area, one by Wyss⁷ in 1871, the other by Sattler⁸ in 1875. The former found extravasation of blood into the inner aspect of the Gasserian ganglion, and into the beginning of the first division of the trigeminal nerve, accompanied by a purulent inflammation pushing the ganglion cells apart. In the case of Sattler, a man aged 85, a few days after he was poisoned by carbonic oxid gas, developed herpes ophthalmicus. Death occurred 14 days afterwards and the Gasserian ganglion was found to be infiltrated with round cells, and there was marked destruction of the ganglion cells. Until 1900 there had been five satisfactory reports on zoster of the trunk—Lesser,⁹ three excellent cases; Chandelux,¹⁰ one case; and one thoroughly studied case by Dubler.¹¹ These all showed changes in the posterior root ganglia corresponding to the area affected.

Head and Campbell studied 21 cases of herpes zoster in different stages of the disease and associated with various clinical conditions. In a few of these the herpetic eruption was in the distribution of the fifth nerve, the others corresponded to segments at various levels of the spinal cord. The pathologic changes they found may be described under five different headings:

(1) *Changes in the ganglion of the posterior root:* Here they found an extremely acute inflammation with exudation of small, deeply staining, round cells; extravasation of blood; destruction of ganglion cells and fibers and inflammation of the sheath of the ganglion. The lesion was always situated in the dorsal aspect of the ganglion, i. e., in that portion opposed to the anterior root. If not severe the inflammation may pass away, leaving no recognizable change in the ganglion, but in the severer cases permanent changes in the way of scarring, which occupy from one-sixth to one-half of the ganglion, remain. Within this area all the ganglion cells are destroyed and no structure remains to show where they once existed. In a few cases, occasionally healthy ganglion cells may be seen scattered here and there throughout the scar tissue. Over this scar the sheath of the ganglion is considerably thickened.

(2) *Changes in the posterior nerve roots:* From 10 to 11 days after the eruption first appears changes are demonstrable in the posterior nerve roots. The degeneration here is of the usual acute type, with disintegration of the myelin sheath, and if the process is severe fibrous tissue may take the place of the nerve fibers that have been destroyed. If the lesion has been mild the products of acute destruction may disappear leaving no recognizable changes. In one case, however, well marked sclerosis, affecting one-half of the posterior nerve root, could be detected as late as 272 days, and in another case 790 days after the disappearance of the eruption.

(3) *Changes in the peripheral nerves:* The changes in the peripheral nerves probably begin about the same time as the degeneration in the posterior nerve roots and show the same disintegration of myelin sheath and subsequent sclerosis. Both anterior and posterior primary divisions are affected, but the number of degenerated fibers is always greater in the latter. The sclerosis once established is permanent and has been shown to exist as late of 790 days after the herpes had disappeared.

(4) *Changes in the spinal cord:* If the cells of the posterior root ganglion are destroyed experimentally we get an acute degeneration of those fibers, which, entering the spinal cord by the posterior root, pass upwards in the posterior columns. Thus, in the inflammatory lesions of the ganglion with destruction of its cells we see a corresponding degeneration of the fibers in the posterior columns, and in cases in which the eruption is on the arm, the degeneration can be followed up to the nucleus cuneatus. The degeneration in the spinal cord appears about the ninth or tenth day after the eruption, and if the lesion is extensive the nerve fibers may be replaced by fibrous tissue.

(5) *Changes in the skin and glands:* A section made through an unruptured vesicle of herpes zoster shows a cavity, the floor of which is formed by naked papillæ. These are in a condition of profound inflammation and are infiltrated with masses of deeply staining round cells. The vesicle is split into incomplete cavities by septa, extending from the roof of the floor. The cavity is filled with fluid which coagulates into a somewhat granular hyaline mass. The lymphatic glands in the neighborhood of the herpetic eruption enlarge and become quite tender.

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Wright's Vaccine Therapy, with Report of Cases

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About six years ago, Wright, of London, first proposed a new treatment of certain infectious diseases by bacterial inoculation. This caused a great deal of discussion, but did not arouse widespread interest in America until three or four years later. The work reported here was undertaken with three ends in view: to test the efficiency of this treatment; to test the accuracy of Wright's method of ascertaining the opsonic index; and to determine whether or not the estimation of the index was necessary for carrying out the treatment.

Perhaps it might be well to say just a word about the original technic that Wright advocated. His whole theory rests upon the assumption that for phagocytosis the presence of blood serum—or at least a certain substance in the serum—is necessary. He proved this experimentally, and devised a method for measuring the quantity of this substance in the serum. This method he describes essentially as follows: A certain amount of blood, collected in sodium citrate solution to prevent coagulation, is centrifugalized until the red cells lie at the bottom of the tube and the majority of the leukocytes form a cream-like layer on top of them. The supernatant citrate solution, containing most of the plasma, is removed and the corpuscles washed with salt solution till *all* the plasma has been removed. Next he makes a suspension of the organism in question, in salt solution. Lastly, he secures some of the patient's serum. Proceeding to make the determination he measures equal volumes with a capillary pipette from each of these three solutions, viz: one volume of corpuscles from the leukocytic cream, an equal volume of the bacterial suspension, and an equal volume of the patient's serum. These three volumes are mixed thoroughly, and finally the whole amount is taken up into the pipette and the end of this sealed in the flame. The whole process is then repeated with the one difference of using *normal* serum in place of the patient's serum. The two pipettes are then incubated together for 15 minutes after which slide preparations are made from each. The number of bacteria contained in, say, 100 leukocytes from each pipette are then

counted under the microscope. The two preparations are identical, except that in one case the patient's serum is used and in the other a normal serum; therefore, the count establishes a direct ratio between the power the patient's serum has to cause phagocytosis and that of normal serum.

This technic and the results obtained have been called in question a great deal. *A priori*, a number of things suggest themselves as possible sources of error. First, measuring. The accuracy of drawing out the fine pipettes may be uncertain. So, heavy barometer tubing was employed and the pipettes standardized carefully with mercury under a magnifying lens. Secondly, the taking of equal volumes assumes a perfectly uniform suspension of both corpuscles and bacteria. In order to ensure this, the red and white corpuscles are thoroughly mixed again, after washing away the plasma, and probably a more even distribution of leukocytes thus obtained. In the case of the bacteria, the clumps are broken up by shaking the suspension with glass beads, like that in the mixing chamber of a blood-counting pipette, and the suspension then reduced to the requisite thinness by centrifugalization. Third, a further point in which it seemed as if the old technic might be at fault was, that while the contents of the pipette containing the normal serum was being mixed the other was lying at one side at room temperature. This would probably induce a certain amount of phagocytosis. More certainly, *after* incubation, phagocytosis would go on in one pipette, warm as it would be from the incubator, during the time the slide preparations were being made from the other pipette. To avoid this, a dish of cold water is provided into which the unused pipette is plunged while the other is being manipulated. Fourth, Wright himself mentions the difficulty encountered from the iso-agglutination of the red corpuscles by certain sera. It is hoped that this may be avoided by the use of unusually fine capillary pipettes for incubation, so that the serum will still come into fairly uniform contact with all the bacteria, even if a slight agglutination takes place. This has not yet been fully worked out. To sum up—this technic has differed from Wright's in the following particulars: (1) Adoption of measuring pipettes standardized by mercury; (2) Additional attention to the obtaining of uniform suspensions of corpuscles and bacteria; (3) Instantaneous stopping of incubation by cold water immersion when pipettes are removed from the incubator; (4) Fine capillary tubes for incubation.

Just a word as to results. There are 376 indices in this series. Of these, 48 must be disregarded as not having any check upon them. Of those that did have a check upon them, 224 checked up well, some to the third decimal place; 104 did not. These figures include indices done before the technic was modified, and of those more than 60% failed to check. In attempting to check the work, four separate determinations were made each time an index was done. There being two workers, each one made two determinations, thus checking both the other's results and his own. It was considered a check when the results tallied to within *one* in the first decimal place.

In the preparation of the vaccines themselves no changes have been made except to include glass beads in the bottle to facilitate even distribution of bacteria by shaking. A salt solution suspension of the bacteria is made and sterilized by heat—60°-65° C. for an hour. This vaccine is first standardized by mixing a minute volume of it with an equal volume of normal blood. From the mixture slide preparations are made, and 1000 red cells counted under the microscope aided by an Ehrlich's eyepiece. The number of bacteria met with during this counting is also noted. This establishes at once the ratio of bacteria to red blood-cells and as the number of red cells per c.c. is known the approximate strength of the vaccine—*i. e.*, the number of organisms it contains per c.c.—may be figured at once.

In the following report of cases it will be impossible at this time to give more than the briefest summary of our experiences with bacterial vaccines. In order of frequency, the microorganisms used were, *Staphylococcus albus* and *aureus*, *gonococcus*, *Bacillus coli*, and *streptococci*. We have not attempted to work with *Bacillus tuberculosis* on account of the difficulty in making even emulsions for the determination of the opsonic index and because of the time required before clinical improvement could be noted. For purposes of convenience the cases treated will be classified according to the microorganism isolated from the infectious processes.

Staphylococcus albus infections.

Acne: Altogether we have treated 28 cases of acne. These for the most part were not mild cases, but the patients had tried the various lotions, operative measures, etc., at the hands of various physicians, and had been sent as a last resort to receive vaccine treatment.

Varying results have been reported by different observers as regards the efficiency of *staphylococcus* vaccine in the treatment

of this disease, and the consensus of opinion seems to be that while marked improvement often results, nevertheless the acne is not permanently cured.

This should have been expected when one realizes that the disease is, in all probability, primarily due to a bacillary infection and secondarily due to a staphylococcic infection. Unna, Gilchrist and others have called attention to the fact that in the earliest lesions of acne the acne bacillus is found, usually in pure culture. Later on, however, when pustulation occurs, these bacilli may still be present in large numbers in pure culture, in small numbers and disintegrating together with the staphylococcus or the staphylococcus alone may be present. It would seem unreasonable to expect to control, by the use of *Staphylococcus albus* vaccine alone, anything more than the staphylococcic part of the infection. We have been able to corroborate Gilchrist's findings as regards the bacillary nature of acne and have never failed to find the *Bacillus acnei* in the pultaceous material expressed from the primary acne pimple. Examination of smear preparations made from blackheads taken from nearly 100 different individuals again confirms the statement that these bacilli are present in large numbers and in practically pure culture, staphylococci being present only when pustule formation develops, and by no means always present then. Again the opsonic index to *Staphylococcus albus* in early, though marked, acne is as a rule nearly normal, being usually .8 or .9. When marked pustulation is present and secondary infection with *Staphylococcus albus* takes place the index may become very low to *Staphylococcus albus*.

Reasoning on this basis that acne is, as a rule, a combined infection, we have treated it as such, using a combined bacillary and *Staphylococcus albus* vaccine with results which are most encouraging when one considers the class of cases treated. Unfortunately it is most difficult to cultivate the *Bacillus acnei* in amounts suitable for making vaccine and it is practically impossible to obtain autogenous vaccine in most cases. We, therefore, have used a stock bacillary vaccine and, when possible, an autogenous *Staphylococcus albus* vaccine, with the result that six cases are apparently cured, nine cases markedly improved and two cases unimproved. In these last two cases we were unable to get any growth though pimples were repeatedly opened and coverslip preparations showed the presence of the *Bacillus acnei* in pure culture. Five cases show definite improvement and

are still taking treatment, though it is too soon to speak with any degree of positiveness as regards the ultimate outcome. Six cases did not come for treatment with any degree of regularity and, after receiving a few doses of vaccine, failed to continue treatment and so can not be considered in this report.

Staphylococcus aureus.

Furunculosis: We have treated seven cases with most gratifying results in all. *Staphylococcus aureus* was the organism isolated in each instance and autogenous vaccine was prepared for each case.

One patient who had been for two years the subject of chronic furunculosis, the boils having appeared with great regularity every two or three weeks, received prompt and permanent relief following the first dose of vaccine. Treatment was continued, however, for several weeks in order to guard against a possible relapse, with the result that no more boils have appeared, over a year now having elapsed since the last treatment.

A discharging sinus following infected inguinal glands with chronic leg ulcer and furunculosis of six months standing, from all of which lesions *Staphylococcus aureus* was isolated, yielded promptly to vaccine therapy. In a case of Ludwig's angina, from which at operation *Staphylococcus aureus* was obtained in pure culture, the brawny induration subsided and marked clinical improvement was noted, complete recovery following one dose of autogenous vaccine.

Two cases of sycosis barbae non-parasitica were treated with mixed vaccines, with slight improvement in one case, though little benefit was noted in the other.

Gonococcus.

In 11 cases of gonococcus arthritis, in which stock vaccine was used, it was our own opinion, as also that of other physicians who followed the cases, that the improvement was more rapid and satisfactory with vaccine therapy than without it. In several cases of posterior urethritis, in which the patients had sensations of heat and discomfort, relief was obtained from the symptoms following the use of gonococcus vaccine though the shreds in the urine persisted.

In two of three cases of gonorrheal vaginitis in children the discharge promptly ceased when vaccine therapy was tried. In the third case improvement was noted but not a cure.

Streptococcus.

In two cases of endocarditis a diplococcus was isolated resembling that described by Poynten and Paine as the cause of acute articular rheumatism and malignant rheumatic endocarditis. Following the use of small quantities of a vaccine made from this microorganism, in one case marked relief of pain in the joints resulted and twice, following the use of the vaccine, the temperature fell to normal and remained normal for nearly 48 hours afterwards, though the temperature had been septic in character previous to vaccine therapy and again became so subsequently.

No permanent improvement was obtained but simply enough to suggest the possibility that perhaps, if resorted to early enough, vaccine therapy might be of great value in the treatment of this otherwise unsatisfactory condition.

In two cases of arthritis deformans the urine contained large amounts of indican and in one of these cases the patient had experienced such great relief from joint pains when suffering from ptomaine poisoning with an associated gastro-enteritis, that it seemed worth while to investigate the intestinal flora with a view of determining whether any organism was present which might bear some etiologic relationship to the joint condition present. We were somewhat surprised to find a streptococcus present in large numbers in both instances. The patients' opsonic indices were normal to *Bacillus coli*, but increased to this streptococcus. A vaccine was then prepared and administered in small doses to both patients. At times there seemed to be some relief ascribable to injections but nothing definite can be stated at this time as regards improvement.

Bacillus coli.

Eight cases of infection of the urinary tract with *Bacillus coli communis* were treated with autogenous vaccine with marked benefit so far as the general condition of the patients was concerned. One woman, afflicted with pyelocystitis, had been catheterized at regular intervals both day and night for months owing to her inability to pass urine voluntarily. After the third injection of vaccine the urinary condition had so far improved that micturition was accomplished in normal fashion and the urine was freed from the large amount of pus previously present though it was still definitely turbid. The mental condition of this patient, manifestly hypochondriacal when she was first seen, was markedly improved. A little girl was admitted to Lakeside Hospital with cystopyelitis, clinically resembling typhoid fever.

Following the first dose of vaccine she had a normal temperature and rapidly regained her customary good health.

In one case of bacilluria of seven years' standing no improvement was obtained by the use of urotropin. Vaccine therapy was employed with marked though not absolute clearing of the urine. Urotropin was again resorted to and still further improvement was noted. At present the condition is somewhat variable, at times the urine being quite clear and then again moderately turbid though definite progress toward recovery has been made.

Marked improvement in the general condition of the patient with a lessening of purulent discharge and lowering of the septic type of temperature has followed the use of autogenous vaccine in the following cases: Subphrenic abscess following ruptured appendix. Localized peritonitis subsequent to appendiceal abscess formation. Pyelocystitis associated with stone in the kidney. Pyelocystitis: in this last case one kidney had been removed for an infected malignant growth.

From this brief summary of our cases we think we are justified in concluding that undoubted benefit can be obtained in selected cases by the judicious use of so-called bacterial vaccines. The results in chronic furunculosis are most satisfactory. Most cases of acne are strikingly improved if not actually cured. The marked improvement in the patient's general condition in infections of the urinary tract with *Bacillus coli communis*, together with a more clear if not entirely clear urine, makes it worth while to use vaccine as an adjunct at least to other methods of treatment and especially so if urotropin fails to give satisfactory results. The use of vaccines is helpful also to the surgeon in the postoperative treatment of suppurative abdominal and other conditions. Autogenous vaccines should be employed when possible because the results are more satisfactory, and particularly when dealing with infectious processes due to *Bacillus coli* and streptococci, as there are so many different strains of these organisms. As regards dosage, each patient is more or less an experiment in himself. The smallest dose that will give therapeutic results is the one to use and it should be continued for as long a time as definite improvement is noted. When the improvement lags, an increase in the size of the dose or in the frequency of injection is usually indicated. Probably some of the bad results obtained with opsonic therapy can be satisfactorily explained on the assumption that too large doses were used.

Formaldehyde Poisoning—With the Report of a Case.

By JOHN MacLACHLAN, M. B., Resident Physician, Lakeside Hospital, Cleveland.

Formaldehyde has become so commonly used as a germicide and disinfectant and is so readily obtainable that cases of poisoning, accidental or otherwise, from the ingestion of its solution might be expected to occur with some frequency. The catalog of the Surgeon-General's Library and the Index Medicus, to date, give references, however, to only 10 such cases, four of which were fatal ones.

In presenting the report of the case which came under the writer's observation it has seemed desirable to review this literature and with the data available attempt to sketch the symptomatology of formaldehyde poisoning. The previously reported cases, with the present one, 11 in all, are as follows:

Case 1. ANDRE¹—Recovery:

Female, took one drachm of a 40% solution of formaldehyde in mistake for tonic. Had immediate, severe, abdominal pain. Within five minutes after taking the poison was given several teaspoonfuls of acetate of ammonia, then an emetic. Had only slight epigastric discomfort, which disappeared in two days.

Case 2. BOCK²—Fatal:

Imbecile male, aet. 26, drank three ounces of a 40% solution of formaldehyde. Immediately vomited blood-tinged mucus and had severe epigastric pain. Demulcents and apomorphin given at once, with free emesis. Continued weak and vomited repeatedly. Sixteen hours later pulse first weakened. In statu quo until the twenty-ninth hour when the heart failed rapidly until the thirty-second, when cyanosis, coma and death occurred. Autopsy showed marked erosion of the lower end of the esophagus. The stomach wall and duodenum were very much congested and cut like leather. Microscopic examination not made. Other findings not abnormal.

Case 3. PALMER³—Fatal:

Male, aet. 29, invited a friend to drink with him. The friend, who had just finished a meal, took whiskey and a little water (which turned out to be formaldehyde in a soda-water bottle); he had severe pains and

Read before the Lakeside Hospital Medical Society, June 30, 1909.

vomited immediately but suffered no ill effects. The patient, who had not eaten for six hours, took a small amount of whiskey and filled his eight-ounce tumbler out of the same bottle; intense abdominal pain and collapse followed. When admitted to the hospital he was tender over the epigastrium, vomited blood-tinged fluid, was slightly delirious and had a marked feeling of constriction of the throat. He was given a dilute solution of ammonia followed by demulcents. Next day his mind was wandering but he was in no special pain. Two days later he became markedly delirious, noisy and at times maniacal. During one of these attacks his pulse failed, his breathing became shallow and his heart stopped. Autopsy showed the blood everywhere dark colored and fluid, mucous membrane of the lower end of the esophagus and the gastric mucosa tanned and parenchymatous organs somewhat congested.

Case 4. BOSE¹—Fatal:

Male, aet. 47, was intoxicated and drank three ounces of a 40% solution of formaldehyde. Found shortly after unable to speak, with hands on abdomen and apparently in great pain. Did not vomit before admission to hospital. After lavage was able to talk rationally. Started to vomit almost at once and continued all that night, the vomitus being blood-tinged. Patient gradually sank but developed no other symptoms and died next day, 13 hours after the ingestion of the poison. Autopsy showed the esophageal and gastric mucosa intensely congested, as was the small and large gut. Some slight changes in the parenchymatous organs.

Case 5. KLUBER⁵—Recovery:

Male, aet. 47, was thought to have had an apoplexy. Remained unconscious 11 hours. It was found that a large dose of formaldehyde had been taken in mistake for Apenta water. Was delirious at times for the next 24 hours and complained, when aroused, of sore throat, headache and lacrimation. Had an anuria for 19 hours. Was given lavage and copious draughts of alkaline waters. Recovery in two days.

Case 6. ZORN⁶—Recovery:

Male, aet. 44, drank 15 c.c. of a 40% solution of formaldehyde in mistake for water. At once drank a tumbler of milk. Violent retching and vomiting followed with dyspnea, vertigo and severe gastric pain. Lavage administered at once. Collapse followed, with an anuria for 24 hours. During second day there was violent tenesmus, diarrhea and some epigastric discomfort. Recovery complete in four days.

Case 7. ZERLACH⁷—Recovery:

Female, aet. 21, swallowed some 60-70 c.c. of a 35% formaldehyde solution that had been given her to dilute and use as a douche. Found unconscious and aroused with great difficulty. Stomach washed out. Stuporous for 15 hours. Anuria for 12 hours. Next day complained of vertigo and had an offensive diarrhea. Urine showed formalin and albumin. Recovered by third day.

Case 8. LENISON⁸—Fatal:

Male, aet. 60, while intoxicated took three ounces of a 40% solution of formaldehyde. Was found writhing in pain and unable to speak. Did not vomit even after 3/10 gr. of apomorphin. Lavage attempted but the tube could not be passed on account of spasm of the pharynx. Died of

cardiac failure in 29 minutes after taking the poison. Autopsy showed the esophagus, stomach and small gut literally "hardened."

Case 9. HUMPTON & LINTZ⁹—Recovery:

Female, aet. 33, was given a pint of 12.5% solution of formaldehyde as a colon irrigation in mistake for a weak silver nitrate solution. She first complained of severe burning in the rectum. Pain in the abdomen, pallor and cardiac arrhythmia followed rapidly and the patient went into collapse. Stimulants and saline enemata improved the condition. Violent diarrhea with tenesmus and vomiting supervened. Anuria for 24 hours. Urine showed blood and casts. Vomitus contained blood. Gradual recovery in two weeks.

Case 10. BOWER¹⁰—Recovery:

Female, aet. 20, swallowed half an ounce of commercial formalin. Seen in 20 minutes, when she was not complaining of any pain. Gastric lavage was immediately done and she collapsed. Afterwards she complained of pain in the throat. Vomited blood-tinged material. Patient lay in a stuporous state for 36 hours and gradually recovered within seven days. No kidney disturbance.

Case 11. MACLACHLAN—Recovery:

The patient, a small boy, three years old, was admitted to Lakeside Hospital, October 19, 1908, under the care of Dr J. H. Lowman.

He had been given a tumbler of 40% formaldehyde in mistake for Poland Spring water and after taking one swallow, choked, but his father, thinking that it was the boy's usual distaste for water, insisted that he drink more. The patient attempted it again when he was seized with a violent coughing and choking spell and fell unconscious at his father's feet. When seen in the accident ward some 20 minutes later, he was still unconscious with a pulse of 160 and respirations 45. Before any attempt was made to give any treatment the patient vomited several ounces of mucus that smelled very strongly of formaldehyde.

Gastric lavage was at once performed with water, followed by milk, eggs and several pints of olive oil. He immediately regained consciousness and complained of pain in his stomach and a sore mouth. On examination the buccal mucous membrane was intensely red and the lips, tongue and pharynx were covered with greyish eroded patches. There was also a marked salivation. When he was later admitted to the ward, he was given strychnin sulphate, gr. 1/60, q. 4 h., and normal saline enemata by the drop method. In the evening the temperature was 103.5 F., pulse 140, respirations 38, leukocytes 7800, hemoglobin 95%.

Oct. 20, 1908: Patient vomited mucus repeatedly all night, but had only one stool which had a marked odor of formaldehyde. Urine voided during the night showed an acid reaction, a slight trace of albumin, no casts or blood, but a marked trace of formic acid was present according to Liebermann's phenol test.

Oct. 21, 1908: Temperature 100° F., pulse 120, respirations 24. Condition improved, no diarrhea or nephritis. Stool and urine both showed formaldehyde. Patient was quite comfortable and took milk by mouth, although he complained of some pain on swallowing.

Oct. 22, 1908: There was no trace of formic acid or albumin in the urine. Swallowing was still painful, but the condition was such that

the child was taken home by the parents and made an uninterrupted recovery.

Reviewing the *toxic symptoms* presented in the reports of these cases, epigastric or abdominal pain, immediate and severe, was the most constant initial symptom, as in all irritant poisoning, followed by repeated vomiting of blood-stained mucus. Rapid loss of consciousness occurred in three of the cases, all of which recovered. Kluber's patient remained unconscious for 11 hours and was at first thought to have had an apoplectic stroke. Bower's patient lay in a stuporous state for 36 hours. One of the fatal cases, a man of 60, died in 29 minutes after taking three ounces of formalin when intoxicated, and though there was great pain and collapse, consciousness was apparently preserved. Sudden death from the ingestion of formalin was found by Fischer²¹ and other investigators to occasionally occur in animals, and the former especially notes the fact that "formalin belongs to that rare class of poisons which are capable of producing death suddenly when swallowed." In the other three fatal cases death supervened in from 13 to 48 hours with rapid, irregular pulse, sighing and shallow respiration, delirium, collapse and coma.

In the cases that recovered, besides the epigastric pain and the frequent blood-stained vomiting of material smelling at first strongly of formaldehyde, there was marked prostration and collapse; the skin was pale and covered with cold clammy perspiration; the pulse was weak and irregular. Loss of consciousness, as previously noted, occurred in three of the seven cases and stupor and mild delirium in others. In all but three of the cases there was suppression of urine, not apparently dependent on the strength or quantity of the formalin solution ingested, the anuria lasting from 12 to 24 hours. Blood and casts were sometimes found in the urine and the presence of formic acid was determined in several instances. Diarrhea and tenesmus occurred in three of the cases. In that of the child observed at Lakeside Hospital the stools had a marked odor of formaldehyde. Complaint of sore mouth and difficulty in swallowing was common. Lacrimation was once noted.

The postmortem examinations of the fatal cases disclosed eschars of the buccal mucosa and pharynx; marked esophageal erosions; an extremely acute gastritis, with the stomach wall seemingly tanned into a leather-like consistency; besides various parenchymatous changes in the liver and kidneys. In the face of

these findings and of the severity of the symptoms present in the non-fatal cases one is struck by the rapidity of recovery. All the cases reported were well within a week except case No. 9 in which the formalin was taken by enema and the resulting diarrhea was especially severe.

The fatal dose in three of the cases was in each, three ounces of formalin; in the fourth, a probably much larger but uncertain quantity was taken. In the cases that recovered the dose varied from one drachm to 60 c. c., the latter being the case of a young woman.

The *diagnosis* of formaldehyde poisoning should be readily made early by the smell of the vomitus or of the material washed from the stomach. The stools may also have a strong formaldehyde odor, and formic acid is present in the first urine secreted.

As to *treatment* all authorities agree that formaldehyde is readily and quickly absorbed, no matter how introduced into the body, so that one must act quickly. Lavage with large quantities of water, followed by demulcents were used in nine of the cases. Sollmann¹² and Andre both strongly advocate the administration of diluted ammonia, or any of the ammonium salts, as a chemical antidote as it destroys the local action of the formaldehyde at once. Andre advises the use of ammonium acetate and in his case complete amelioration of the symptoms occurred after the administration of half an ounce of ammonium acetate, with recovery in two days. The excess of ammonia and the resulting compounds should be removed by emetics or lavage. Stimulants, anodynes and bland diet are required and other symptoms should be treated as they arise.

I wish to thank Dr E. F. Cushing for placing all of the literature at my disposal and Dr T. Sollmann for much valuable data.

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THE NOSE AND NASOPHARYNX IN INFANTS AND YOUNG CHILDREN.*

BY J. M. INGERSOLL, M. D., CLEVELAND.

The shape and the relative size of the nose and the naso-pharynx change very much between the time of their development in the embryo and their permanent form later in life. The changes which take place in these structures in infants and young children have a decided influence upon the pathological conditions which may develop in the nose and nasopharynx and make any kind of obstruction in these regions a much more serious matter in young children than in adults.

The Development of the Nose and Nasopharynx.

The nose is primarily a special sense organ. In man, however, its respiratory function has become even more important than the olfactory function. The evolution of the organ of smell may be epitomized in the statement that the olfactory epithelium is a patch of infolded ectoderm with highly specialized cells which are brought into relation with the central nervous system by means of the outgrowth from the latter, of the olfactory lobe.

Early in intra-uterine life the olfactory plates appear just above the oral fossa and owing to the rapid outgrowth of the surrounding tissue these plates become relatively depressed and form the nasal pits (about the twenty-eighth day). The nasal pits are separated from each other by a broad mass of tissue, called the naso-frontal process, which thickens along its lateral margins and forms the globular processes (Fig. 1). At the same time the lateral nasal processes bud out from the nasofrontal process, above the nasal pits and growing downward form the external boundaries of the pits. Inferiorly the pits are directly continuous with the oral fossa.

About the end of the sixth week the nasofrontal process is joined on each side by the united maxillary and the lateral nasal processes and the nasal pits are thus shut off from the oral fossa. The orifices of the nasal pits form the anterior nares and the pits have become short canals opening through their deep orifices, the posterior nares, into the primitive mouth cavity behind the maxillary processes.

*Read before the American Laryngological Society, Boston, Mass., June 1, 1909.

The nasal fossae are widely separated by the broad nasofrontal process but during later development this process narrows down to form the septum and is gradually elevated above the surface of the face. As the nasofrontal process grows narrower, the globular processes are brought nearer together and fusing in the median line, form the premaxillae and the middle third of the upper lip. Dr. H. P. Mosher has shown that the irregular development of the premaxillae is one of the important factors in causing deviations of the nasal septum. The palatal shelves grow toward the median

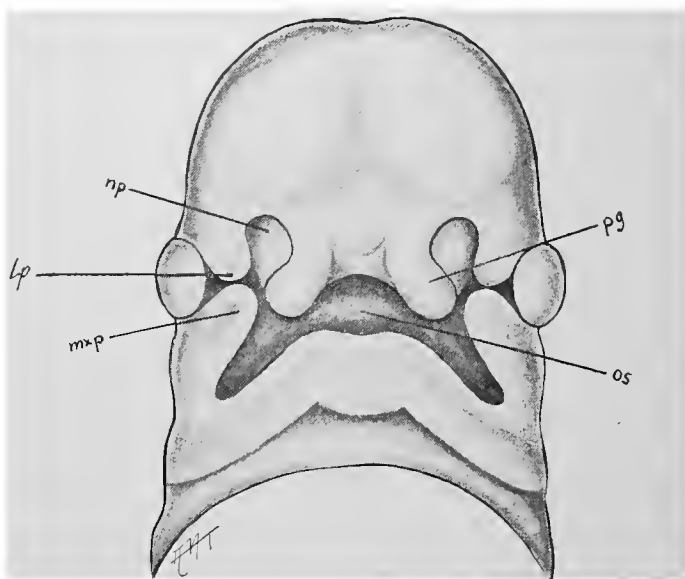


Fig. 1. Face of embryo of 8 mm. (enlarged from His.); m. x. p., Maxillary process; n. p., nasal pit; o. s., oral fossa; p. g., processus globularis; l. p., lateral nasal process.

line and uniting with each other and with the nasofrontal process prolong the nasal fossae posteriorly so that at the end of the third month the posterior nares open into the nasopharynx instead of the mouth.

At least three and sometimes four or five folds of the ectodermic lining on the external lateral walls of the nasal fossae project horizontally inward and form the maxillary and ethmoidal turbinates. Each fold contains a fold of mesodermic tissue which develops into cartilage and later into bone.

The maxillary sinus is formed during the third month by an evagination on the lateral wall of each nasal fossa, between the

maxillary and ethmoidal turbinates. The ethmoidal, frontal and sphenoidal sinuses are formed later and the last two are not completed until after birth.

Very early in the development of the nose a small invagination appears on each side of the median wall of the nasal pits. During the fourth month, this becomes a small pouch in the septum ending blindly posteriorly. This is the rudiment of Jacobson's organ which in macrosmatic animals is much more highly developed, communicates with the mouth and contains olfactory cells, connected with the olfactory lobes of the brain. In the lower animals its function

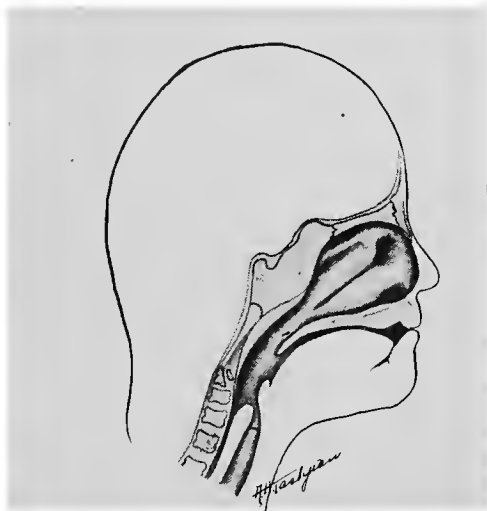


Fig. 2. Section showing the left nasal fossa, nasopharynx and pharynx of a foetus about the twelfth week. In this specimen there are only two ethmoidal turbinates—the aggr nasi shows quite distinctly as a prolongation forward of the ethmoidal turbinate.

probably consists in bringing the food in the mouth under direct control of the olfactory nerve.

Foetus, about the twelfth week, Figure 2. The length of the nasal fossa in a foetus three months old is about 1.4 cm., its height about 0.7 cm. The length of the nasopharynx is about 1.3 cm. and its width between the Eustachian openings, is about 0.5 cm. The floor of the nose is quite straight and slopes downward slightly. The maxillary turbinate shows distinctly as a shelf-like process and touches the nasal floor lightly. The ethmoidal turbinates are well developed and are situated relatively more posteriorly in the nasal fossae so that their anterior ends are about over the

middle of the maxillary turbinates and their position thus corresponds more closely to the position of these structures in some of the lower animals.

The choana is nearly round, its transverse diameter being slightly greater than the perpendicular. The nasopharynx extends down-

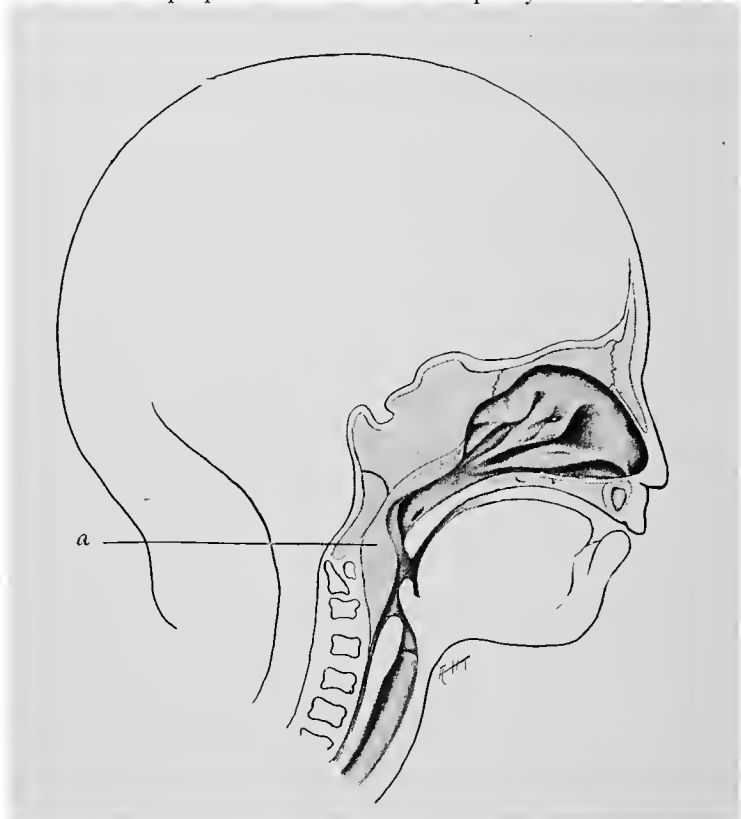


Fig. 3. Longitudinal section, showing the left nasal fossa, nasopharynx and larynx of a six-months old foetus; a—adenoid tissue. The maxillary turbinate is well developed; four ethmoidal turbinates can be seen; the nasopharynx contains quite a large mass of adenoid tissue; the inferior border of which extends down below the opening of the larynx.

ward and backward from the nose and is only very slightly curved. The opening of the Eustachian tube is elliptical and is nearly parallel with the floor of the nose. The larynx is relatively very high up being about opposite the second vertebra. The tongue is proportionately much thinner at its base than it is later. The width of each nasal fossa is relatively less than in the adult because the septum in the foetus is much thicker.

Foetus, sixth month, Figures 3 and 4. In a foetus of the sixth month the turbinates are all more prominent and the meati are well marked. The septum is proportionately somewhat thinner and the nasal fossae are consequently a little wider. The maxillary sinus shows distinctly as a narrow cavity, its lateral walls being almost in apposition. Very shallow depressions in the frontal, ethmoidal and sphenoidal bones suggest the beginning of the sinuses in these regions. The nasopharynx is somewhat more sharply curved than it is in a younger foetus. Hypertrophied adenoid tissue may be

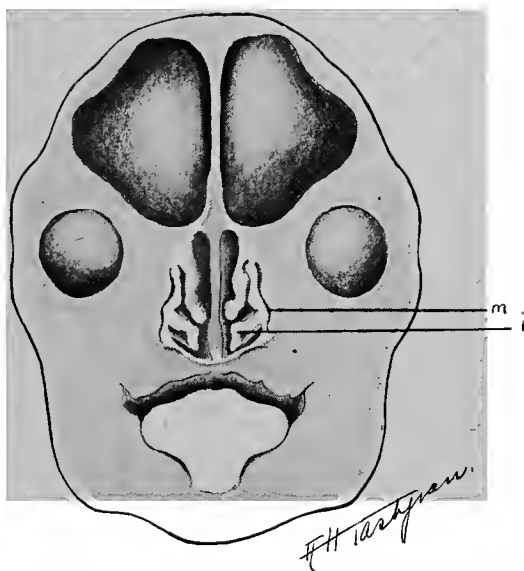


Fig. 4. Transverse section through the head of a foetus six months old, showing both nasal fossae; the maxillary sinuses can be seen as narrow cavities with their walls almost in apposition; m—maxillary sinus; i—inferior turbinate.

present and its relative position is much lower than it is in children and adults so that its inferior portion may extend below the opening of the larynx. The larynx remains relatively high about opposite the third vertebra.

Foetus, eighth month, Figure 5. In a foetus of the eighth month the length of each nasal fossa is about 3.0 cm.; the height about 1.4 cm.; the width about 0.5 cm. The length of the nasopharynx is about 2.4 cm. and its width between the Eustachian openings 1.3 cm.

The turbinates and the meati are sharply defined. The floor of the nose and the soft palate are flat and slope downward slightly.

The nasopharynx curves downward and backwards and its posterior wall presents a smooth, regular outline, if it is free from adenoid tissue. The larynx is about on a level with the upper border of the fourth vertebra.

Child, six months, Figures 6 and 7. In a child about six months old the length of each nasal fossa is about 4 cm., the height is about

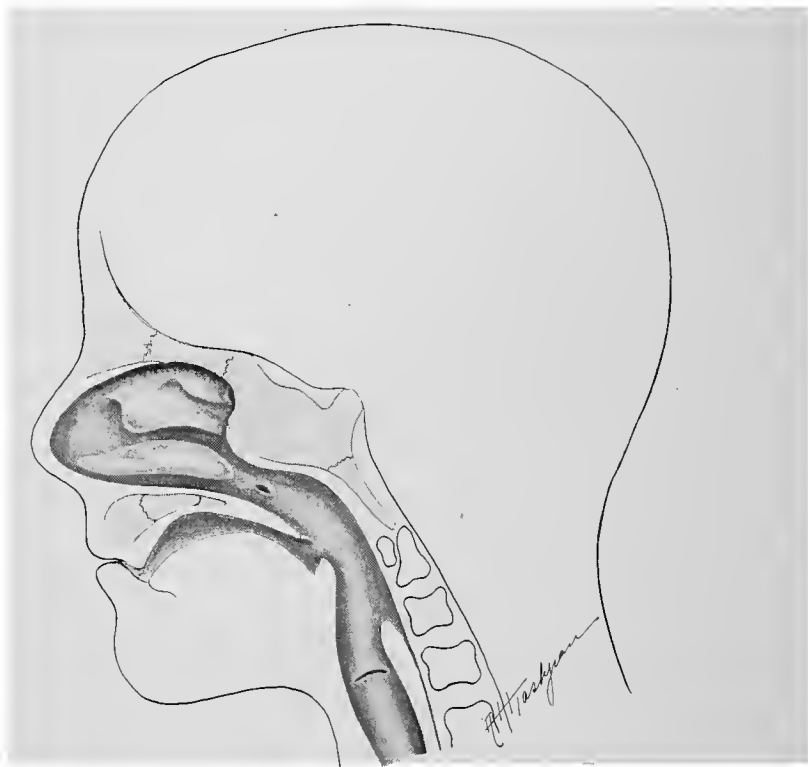


Fig. 5. Section showing the right nasal fossa and pharynx of a foetus about eight months old. In this specimen only two ethmoidal turbinates are present; the nasopharynx is free from adenoid tissue; the elliptical opening of the Eustachian tube is nearly parallel with the floor of the nose.

1.8 cm., and the width 0.7 cm. The width of the nasopharynx is about 1.6 cm. and its length 3 cm.

The general conformation and the relative position of the turbinates are nearly the same as in the adult. The palate is slightly curved. The long axis of the Eustachian opening is nearly parallel with the floor of the nose. The posterior boundary of the nasopharynx is sharply curved. The larynx is about on a level with the fourth vertebra.

If there is much hypertrophy of the adenoid tissue it may obstruct not only the posterior nares, but also the larynx, for the nasopharynx is relatively low and the larynx is relatively high.

Summary. During foetal life and early infancy the relative proportions of the length and the height of the nasal fossae remain about the same—that is, the length is about twice as great as the height. After the second year, the height increases more rapidly. On account of this increase in height of the fossae, the choanae,

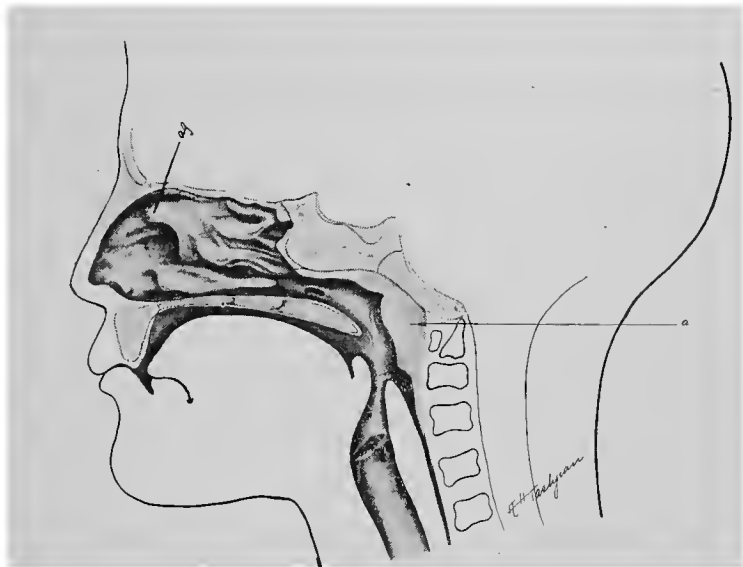


Fig. 6. Longitudinal section, showing the right nasal fossa, nasopharynx and larynx of a child about six months old. The outline of the maxillary turbinate is about the same as in an adult. Four ethmoidal turbinates can be seen. The agger nasi shows distinctly, as a rounded process extending forward from the anterior part of the ethmoidal turbinate. A small diverticulum extending into the sphenoidal bone shows the beginning of the formation of the sphenoidal sinus. The long axis of the Eustachian tube is nearly parallel with the floor of the nose. The nasopharynx contains a rather large mass of adenoid tissue, which extends down below the opening of the larynx. The tongue is relatively thin posteriorly. The larynx is relatively high. A. g.—agger nasi; a—adenoid tissue.

which are nearly round in infants, become decidedly elliptical and the perpendicular diameter of each choana becomes about twice as great as the transverse diameter.

The width of each nasal fossa is relatively less in an infant than it is in an adult and hence any pathological lesion causing nasal obstruction in an infant is a more serious matter than it is in an adult. This is so not only on account of the relatively greater in-

terference with respiration, but also because the nasal obstruction causes decided interference with the taking of nourishment.

The septum is relatively much thicker in the embryo and young infant than it is later in life. The general form of the maxillary turbinate remains very nearly the same during its whole development. The ethmoidal turbinates show many variations. Two are always present; there may be three, four, or occasionally even five ridges which correspond with the much more complicated development of these structures in many of the lower animals. The fourth and fifth ethmoidal turbinates usually disappear in early infancy.

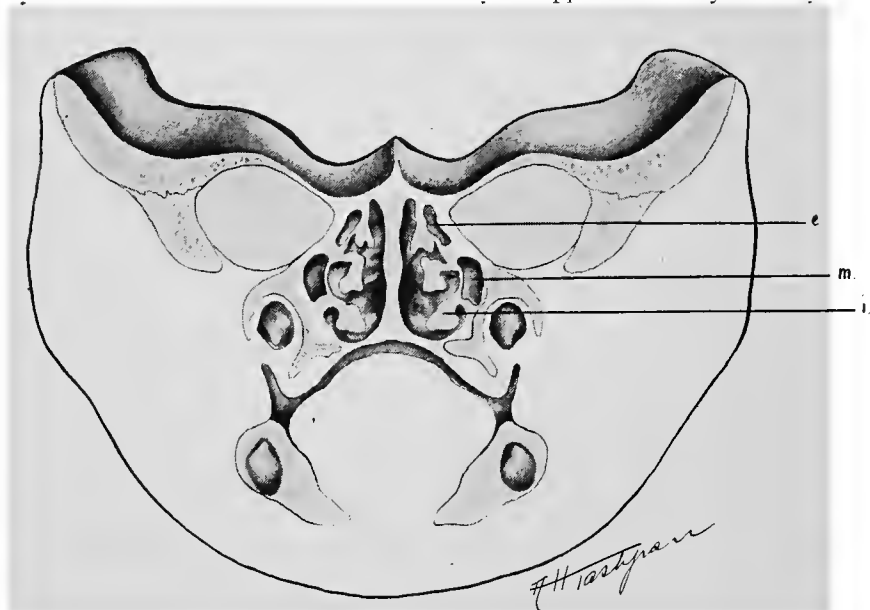


Fig. 7. Transverse section through the head of an infant six months old, showing both nasal fossae. The maxillary sinuses show as rather oval cavities. Two ethmoidal cells show distinctly. E—ethmoidal cell; m—maxillary sinus; i—inferior turbinate.

The third ethmoidal turbinate remains in about eighty per cent of cases.

The agger nasi is a slight elevation at the junction of the anterior end of the middle turbinate (first ethmoidal turbinate) with the nasal process of the superior maxillary bone and is the rudiment of the nasal turbinate of the lower animals.

The maxillary sinus appears about the middle of the third foetal month. The frontal sinus begins as a slight depression extending upward from the nasal fossa in the third foetal month. It is

however, so small that it can hardly be called a sinus until about the seventh year when the true sinus is formed by the separation of the two tables of the skull.

The ethmoidal cells appear first during early foetal life as small depressions which grow by the absorption of the bone. The sphenoidal sinus is primarily a constriction of the primitive nasal fossa and begins to form in the third foetal month. The space is so rudimentary that not until the seventh year has there been sufficient absorption of the cancellous bone to make the sinus apparent.

The organ of Jacobson develops at a very early period and after the fifth foetal month it usually begins to disappear.

The hard palate at birth is about on a level with the junction of the sphenoidal bone and the basilar portion of the occipital bone. At three years it is opposite the middle part of the basilar portion and at six years it is about the same as in the adult, opposite the anterior edge of the foramen magnum.

The soft palate at birth is nearly horizontal and about on a level with the atlas. The tongue is relatively thinner at its base in an infant than it is in an adult.

The nasopharynx at birth is a tube-like structure extending downward and backward. It is relatively long and shallow.

Hypertrophied adenoid tissue may be congenital. If it is present in an infant, it may obstruct the nasopharynx and also the larynx on account of the high position of the latter. The obstruction and irritation of the larynx in this way is probably one of the chief factors in the causation of croup and other lesions of the larynx in children with adenoids. It seems probable also that the relatively low position of the adenoid tissue might make deglutition more difficult. It may be seen in some cases by direct inspection through the mouth if the soft palate is elevated and drawn slightly forward. On account of its relatively low position, it may be easily felt in a careful examination with the finger. The advisability of its removal is self evident, regardless of the age of the child.

The openings of the Eustachian tubes are elliptical and the long axis at birth, is nearly horizontal. The Eustachian prominences are only slightly raised above the surrounding tissue and hence are less liable to be injured in operations in the nasopharynx in infants.

On account of the small oral cavity and the shape of the nasopharynx in infants a curette with a straight handle and its blade set at an angle of fifty-five degrees to the handle will follow the posterior wall of the nasopharynx better and remove the hypertrophied

adenoid tissue more completely than it will if the blade is more nearly perpendicular to the handle as it is in many curettes. The bayonet curette of Fein was devised to permit greater latitude in the movement of the curette and thus allow its blade to follow the conformation of the nasopharynx. The width of the curette blade should be determined, of course, by the width of the nasopharynx. A curette 1.3 cm. in width with a blade 1 cm. in width, is probably small enough for all infants.

The shape of the nasopharynx in infants makes it practically impossible to do a complete adenotomy with forceps.

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Reprint from SURGERY, GYNECOLOGY AND OBSTETRICS, September, 1909.

LATE MANIFESTATIONS OF INTRACRANIAL HÆMORRHAGE OF TRAUMATIC ORIGIN¹

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IN the Surgical Observer of 1816 (page 446, also Guy's Hospital Reports, 1886, page 157), Sir Charles Bell records the following observation: "Strike the skull of the subject with a heavy mallet. On dissection you will find the dura mater to be shaken from the skull at the point struck, repeat the experiment on another subject and inject the head minutely with size injection and you will find a clot of the injection lying betwixt the skull and the dura mater at the part struck and having an exact resemblance to the coagulum found after violent blows on the head. I imagine this is conclusive."

Tillaux, whose lectures I attended twenty-seven years ago, in his *Anatomie Topographique* calls attention in this connection to the fact that the adhesions of the dura to the skull are the least in the temporal fossa at the site of the distribution of the meningeal artery. It has also been shown that the dura is more adherent in youth and advanced age than in middle life.

To go still further back, Mr. J. Hill, in 1751 (*Cases in Surgery*, Edinb., 1772, also Guy's Hospital Reports, 1886, page 187), reports the case of a man about thirty years of age struck on one side of the head with a loaded whip, and on the other side with a crab stick. The next morning he was lethargic and the whole right side was paralytic. There was no fracture or depression. Symptoms showed the necessity of opening both sides of the skull, but the impressions of the staff being strongest on the right side it was opened first, though the symptoms equally indicated the contrary. A large extradural clot was removed. The operation gave relief, but the friends would not permit operation upon the opposite side until four days later, when the case seemed hopeless. Then the other side was opened, and a very large extradural clot was removed. The patient was in good health in 1791, that is, twenty years later.

¹ Read before the Chicago Surgical Society, May 5, 1909.

² For the history of cases I am indebted to my assistant, Dr. Isadore Fuhs.

It is interesting after reading such observations to note the two cases which follow, recorded by Mr. C. Cock in Guy's Hospital Report, 1842. (Vol. vii, page 175.)

A patient fell, injuring the left side of his head. He was brought to the hospital at 7 p. m. in a conscious condition. At 4 a. m. patient got out of bed "for motions" but answered incoherently. At 8 a. m. patient was found entirely unconscious, with stertorous and interrupted breathing. At noon he was trephined and a large clot of blood was removed. Patient recovered and remained well until 1849, a period of eight years, after which epilepsy developed, the patient dying in 1856 from a hæmorrhage at the site of the old injury. At this time he was under the care of Sir Wm. Gull.

A year later the same surgeon, Mr. Cock (*idem*, page 180), reports a case having similar symptoms. He cut down upon the skull at the point of contusion, and finding no fracture, thought best not to trephine. The patient died a few hours later and at the post-mortem a large extradural clot was found.

It seems strange that the success of the first case should not have suggested to Mr. Cock the necessity for trephining in a second case having similar symptoms. It seems stranger still that so many years elapsed before the profession at large came to understand the full significance of traumatic cerebral hæmorrhage, both extradural and intradural or epi- or supradural and subdural, according to the nomenclature one may elect.

To be sure occasional observations were made of epidural and subdural clots, some caused by blows or falls and some by bullets, such as one recorded by Guthrie in the *Peninsular Campaign* (*Injuries of the Head Affecting the Brain*).

The number of cases was, however, small, if we may judge by those which are reported, and advance in knowledge seems to have resulted, in a considerable degree at least, from observations made at post-mortems.

Excellent papers upon the subject have been written by various authors, whose names I need not here record, since many of them are cited in my paper in connection with cases which they have recorded, but most of these papers have been published within relatively recent years.

Notwithstanding all that has been written, the number of recorded operations is small, and to find the special class of cases which I shall place before you to-night a careful search has been made through the literature of the Surgeon-General's library at Washington. I am surprised that so few cases have been found. Doubtless some may have been overlooked.

The experience which first especially attracted my attention to this subject was an operation performed in 1896, and

reported in the Philadelphia Medical Journal, September 16, 1899. It was as follows:

CASE I. J. G. Male. Age 56 years. By occupation a farmer. On May 9, 1896, the patient was kicked by a horse on the right side of the head nearly over the coronal suture. The scalp was cut through and patient was rendered unconscious for a short time, possibly half an hour or an hour at the longest. He recovered and without assistance walked from his barn to his house. The wound was dressed and healed promptly. For two days the patient complained of faintness. About June 17th, he began to complain of headaches, not very severe, but persistent. He had always been free from any trouble of this kind and was an unusually healthy man. From this date the headache continued until the time of operation. It was never very severe, and the patient was unable to localize it. On June 20th, the patient seemed to become dazed and lapsed into a state of indifference, being very quiet and listless, a condition utterly foreign to him. He complained of increasing lack of strength in his right arm and leg, which eventually amounted to partial paralysis. His ability to think and reason became less each day. His bowels were obstinately constipated, he had no appetite, and when undisturbed he manifested a tendency to sleep.

I saw the patient on June 26, with Dr. F. W. Upson of Connecticut. On examination I found that his eyes responded normally to light, that motion was perfect, and that vision was seemingly intact. There was no difference in the pupils. The right arm lay apparently helpless, but when I insisted very strongly, he would, with great effort and deliberation, raise it from the bed. The patient would grasp the hand with considerable firmness. He could move the right leg more freely than the right arm, but still only slowly and with considerable embarrassment. Sensation seemed normal in both right arm and leg. The knee reflex was normal. The left arm and leg were moved promptly. Patient somewhat slow in comprehending what was said to him, but answered accurately all questions. There was a scar about $2\frac{1}{2}$ inches long extending from the frontal region upward and backward at about $1\frac{1}{2}$ inches to the right of the sagittal suture, and parallel to it. This marked the point at which the man had been kicked. A curved flap was made with its convexity forward, the flap having a length of from $2\frac{1}{2}$ to 3 inches. Upon lifting the flap no injury could be found to the skull at this point. The skull was penetrated by a trephine, but the dura mater was found to be normal. The brain bulged strongly into the trephine opening. No pulsation could be felt. An aspirating needle inserted in all directions found nothing. A probe carried in all directions under the skull and outside the dura mater disclosed no roughness. It was, therefore, decided to trephine on the opposite side of the skull in the region of the arm center. I trephined upon the right side first, because the external injury had been at this point. The difficulty in moving the right leg, and more especially the right arm, indicated an operation upon the left side of the cranium. The scar upon the right side, however, was so distinct and the injury had been so severe that it did not seem warrantable to disregard it. Thus, the first opening was made contrary to the direct indications of the case as derived from localization symptoms.

Upon laying bare the skull by the same method as had previously been done upon the right side, a blue point could be seen, as of venous blood, shimmering through the external table. There was, however, no fracture. The pin of the trephine was inserted at this point and there was profuse hemorrhage of venous blood. Upon division of the skull this bleeding largely ceased. The dura mater was seen to be somewhat thickened and more dense than normal. Upon division of the dura there was an escape of a large amount of liquefied blood of dark color. After this, many clots were evacuated. The whole amount evacuated must have been from four to six ounces. The

brain was pushed away from the skull sufficiently to accommodate the accumulation of blood, and the removal of the latter left a considerable cavity in the parietal region. The cavity was thoroughly drained by turning the patient upon his side and wiping it out with a sponge. The pia mater seemed to be intact. The cavity was drained with a short piece of rubber tubing, and a small amount of iodoform gauze was inserted. Both wounds were dressed with iodoform gauze and a bandage was applied. The patient's condition at the close of the operation was good. After the operation the patient slept almost continuously for thirty-six hours. The wound discharged a large amount of serum, but healed by first intention, except at the point of drainage. The attending physician reported that reaction after the operation came on slowly. For some time after the operation the patient was unable to articulate distinctly, and swallowed with difficulty, but his mind was perfectly clear. The partial paralysis of the right side was entirely relieved and the patient used his limbs freely. Very large quantities of serum escaped from the wound, estimated by his physician as "One quart in twenty-four hours." The patient's health was restored to normal and he remained well for about nine years. After this the patient complained of headache, lost flesh, grew gradually weaker and his memory gradually failed, and he died in January, 1908, nearly twelve years after his injury.

CASE 2. It was not until recently that I saw a similar case to the one just recorded. In January last (1909) my friend, Dr. Ashmun, telephoned that he had a patient who about two months previously had had a fall, and that recently he had presented symptoms referable to that injury. Recalling my previous experience I replied that I suspected subdural hemorrhage, and advised that the patient be sent to the hospital at once. The case was complicated by the fact that the patient was in delicate health and all his urine had for several years been withdrawn with a catheter. The patient was sent to the hospital at once, where the following history was obtained:

On November 11, 1908, in descending from a street car the patient fell striking on the left side of the head. This caused some abrasion over the outer portion of the left frontal bone. The injury was apparently slight. He was picked up by a passing auto in a dazed condition. He was able to stand, but could not talk, although when asked his name he was able to spell it out, but could not pronounce it. He asked, however, to whom he was indebted for the kindness in picking him up. It was a short time before he could tell where he lived. On reaching home, one hour after the injury, the left eye was closed on account of swelling and ecchymosis and he vomited considerable blood. This was due to a cut in the mouth. There was no bleeding from the ears. There was slight ecchymosis of blood at the outer canthus of the left eye behind the conjunctiva. No defect of hearing. By 9 o'clock he was conscious, although perhaps slightly dazed. At this time the patient could move both arms and both legs. Speech was difficult. He remained in bed for about one week and did not leave the house for about five weeks. Activity was limited by the fact that in the right eye he had a cataract and the left eye was closed by swelling. During this period he was entirely clear mentally. After five weeks the patient walked a considerable distance to the physician's office and later took a street car and went downtown to have his glasses refitted. He remained in apparently normal condition, although being perhaps somewhat depressed mentally, until January 7.

On January 8, while walking across the room, the patient's wife noticed that he stumbled against a chair, and she remarked that his new glasses were not effective. He replied, "No, they do not help me any more than the old ones." The next day, while walking on the street, his wife noticed that he stumbled slightly. On Sunday, January 10, she noticed that he held his fork and spoon in the left hand,

instead of the right, as was his custom. The condition gradually grew worse, so that by Wednesday morning, the 13th, it was necessary to feed the patient.

He was able to pass a catheter until Thursday, the 14th, but he required assistance, and after this he was not able to pass it at all. Before Sunday, the 16th, he had complained somewhat of headache, at times holding his head with both hands. When friends came in to see him he would brighten up and seem natural, but after visitors left he complained of increased pain in the head.

The patient entered the hospital January 16, 1909. The physical examination was very hurried, since the condition of the patient seemed to demand immediate interference. His eyes were open, but apparently he saw nothing. Both pupils reacted to light. It was impossible to make a satisfactory examination of the sensory nerves on account of the mental condition of the patient. The right arm was partly flexed. When told to move it he did so only after the lapse of some time and then moved it very slowly and to a very limited extent, the motion being made seemingly with very great effort. On attempting passive motion of the right arm and leg decided resistance was encountered to either flexion or extension. When the right arm or leg was lifted from the bed it would fall heavily and in its flexed position. There was no apparent change in the tendon reflexes except possibly a slight increase in that of the right patella. Motion of the left arm and leg was normal.

The patient was operated on at once. The left parietal region was exposed by a curved incision and the skull was penetrated with a burr drill just above the temporal muscle. On exposing the dura no discoloration could be seen. After incising it a bloody fluid, having the appearance of venous blood, somewhat diluted with serum, was expelled by successive pulsations, evidently due to the pulsations of the brain. The amount of fluid thus expelled must have amounted to at least six ounces. An instrument inserted into the opening could be carried down in every direction for a distance of from $1\frac{1}{2}$ to 2 inches. After enlarging the opening and washing out the cavity with saline and drying it with absorbent gauze, the brain could be seen pushed back from the parietal bone, flattened and covered with pia mater, but not lacerated as far as could be seen. There were some plates of coagulated fibrin on the anterior surface of the dura mater, but none could be seen on the pia mater. The hemorrhage was easily controlled except at one point. This apparently came from the meningeal artery close to its orifice from the bone, and as it did not seem possible to secure it by ligature, a clamp was placed upon it, clamping the dura mater against the bone. A cigarette drain was inserted into the bony opening, but was not carried inside of the skull. The integument was then sutured except for the exit of the cigarette drain and the forceps upon the meningeal artery. An abundant dressing was applied in order to absorb all discharge.

The subsequent history of the case presents some points of interest. While recovering from the anæsthetic the patient struggled considerably and seemed to use the arms and legs on both sides equally well. Within an hour after operation, while the movements of the right arm and leg were somewhat slow, they were made with a definite purpose. The patient was able to speak in sentences and that evening he said he felt well, and would smile when spoken to. On the morning following the operation the patient spoke in sentences and recognized his attendants. He made mistakes, however, in pronouncing some words.

The first dressing was made on the 18th, when a large amount of serum escaped. On the 20th, the patient, who is an engineer, gave intricate mathematical formulæ with reference to friction.

On January 21, the dressing was changed the second time and it was thought wise to omit the cigarette drain.

The patient's condition remained satisfactory until January 24, three days after the removal of the drain, when in the afternoon he became mentally confused. At 8 p. m. he got out of bed and wanted to go home. At this time the right arm became flexed and somewhat rigid. This condition continued on the next day. He was markedly confused mentally, the right arm remained flexed and the thumb was flexed definitely into the palm of the hand. There was an absence of knee jerk, ankle clonus, Babinsky or other tendon reflexes upon the right side. The reflexes on the left side could be occasionally elicited, but they were not regular. In dressing the wound a pair of dressing forceps were inserted through it into the cavity formerly occupied by the hæmorrhage. Several ounces of serum escaped. A cigarette drain was reinserted and its use was continued in subsequent dressings until the escape of serum had ceased and the wound had nearly closed. With the removal of the accumulated serum the symptoms of compression which had returned, ceased, and the further progress of the case was satisfactory in every way. The patient was soon up in a wheel-chair and went to his home, and he is now, May 5, in his usual health.

The invitation to read a paper before this body came shortly after operating upon this second case. My interest in it was such that when asked for the title of my paper I suggested that of traumatic cerebral hæmorrhage. Had I looked into the literature of the subject before this time I question if I should have ventured to discuss a theme which has already received such extensive consideration. Many papers have been written and several careful collections of cases have been made. On looking over the cases, however, I find that there are relatively few in which the symptoms of compression from hæmorrhage have been delayed later than a few hours, or at most from two to three days.

I have myself seen several cases in which the symptoms of compression developed early. The interval before operation in my two cases just reported was 46 days and 66 days, respectively.

In the presentation of this subject for your consideration an arbitrary period, not less than two weeks from the time of injury to that of operation, has been selected. On the other hand only cases of hæmorrhage are included, those of cyst formations being simply referred to, although cysts are doubtless the terminal stage of certain hæmorrhages.

Although it might prove interesting to discuss the whole subject of traumatic cerebral hæmorrhage, this paper will be limited to a consideration of cases of hæmorrhage, both epi- and subdural, without apparent involvement of the tissues of the brain itself, although it is quite probable that in some cases other brain lesions may be associated with those of hæmorrhage. The hæmorrhage may result from a trauma without fracture of the skull, or at most one of limited extent and with little if any depression of bone. That cerebral hæmorrhage may result from slight violence is well known, as well as the fact that the hæmorrhage may be at the site of the trauma or by contrecoup upon the opposite side of the cranium. The sources of hæmorrhage may be the sinuses, the

vessels of the pia or the brain itself, possibly the diploe, but especially the middle meningeal artery. It is possible that the vessels of the pia may be torn at their entrance into the longitudinal sinus by the violence of a fall, partially dislocating the brain within the cranium.

After entering the skull for a short distance the middle meningeal artery may be wholly enclosed in a bony canal or may deeply furrow the temporal bone and be covered by the dura mater. Steuer says the artery is enclosed in a bony canal in thirty cases out of one hundred.

An examination of 30 skulls which has been made for me shows this condition to exist on one or both sides in 23 cases. The portion of the artery enclosed in the canal is the first part of the anterior branch, the upper limitation of the canal reaching up nearly to the temperoparietal suture. In the upper part of its course the artery lies upon the dura. This close connection of the artery with the bone makes it evident why a blow upon the skull may with slight fracture, or without any fracture, cause a laceration of the artery. Should the meningeal artery be torn without at the same time penetrating the dura mater, an epidural hæmorrhage must result. Should the dura be ruptured by the same violence the hæmorrhage will be between the dura and the pia mater. Rarely both may occur simultaneously.

As cases were collected and studied it became evident that those in which symptoms of cerebral hæmorrhage developed might be cases of either extra- or subdural hæmorrhage.

In the twenty-seven cases collected, in which two weeks or more elapsed between the injury and the operation, all save one were cases of subdural hæmorrhage. One involved the surface of the brain.

The symptoms of extra- and subdural hæmorrhage are similar. Phelps (*Annals of Surgery*, vol. xlv, 1906, p. 807) in an excellent paper on injuries of the head says, "It follows that these two forms of hæmorrhage (extra- and subdural) are not distinguishable from each other. In short, a hæmorrhage is a hæmorrhage, wherever it is situated, and its location can only be indirectly established, if at all, whether it be pial, epidural or cortical."

While this statement is perhaps too strong to meet universal acceptance, and while it is to be hoped that further observation may increase the accuracy of diagnosis, the fact remains that we are as yet unable to diagnosticate definitely as to whether an injury to the head has produced a simple concussion, a hæmorrhage or a laceration of the brain, and Hutchinson remarks that laceration of the brain may give most of the signs of ruptured meningeal artery. In this connection Phelps has pointed out the importance of temperature as a factor in diagnosis. He says (*idem*, p. 802), "The pulse, temperature and respiration must be taken frequently

and systematically. If after the lapse of hours consciousness still remains in abeyance, a stationary temperature but one or two degrees above normal will indicate a hæmorrhage of some profusion without serious central injury; but a higher elevation, which constantly increases, with possible recessions, will point to visceral lesion." He further says (*idem*, p. 808) that the degree of temperature will measure the amount of injury to cerebral tissue, and (*idem*, p. 819) that in a study of more than one thousand cases of intracranial injury there was no instance of recovery when a temperature of 105° was exceeded by the smallest fraction.

It is not the purpose of this paper to discuss cases of extensive injury to the skull, causing damage to the brain itself and accompanied by evident fracture of the vault of the skull with depression, or of the base with hæmorrhage from the ears, etc., but rather those cases in which the injury has as a rule been seemingly slight. Often the patient has simply fallen down, striking the head upon a hard object, or has been struck a light or perhaps a glancing blow. In some, complete unconsciousness has resulted, while in others the patient has been dazed but momentarily.

Mr. Hutchinson (London Hosp. Report, vol. iv, p. 49) has said: "It is certain that the value of the lucid interval before coma as a symptom of ruptured middle meningeal artery can scarcely be over rated. It is worth all the rest put together."

This remark seemingly applies to all intracranial hæmorrhage, the result of trauma and causing slow accumulation of blood, whether the blood be extra- or subdural, and whether it come from the middle meningeal artery, the pia, or the venous sinuses.

A few cases of hæmorrhage have been reported in which no lucid interval has followed the receipt of the trauma, but these cases are rare.

In almost all cases the unconsciousness, total or partial, produced by the trauma has been followed by a lucid interval partial or complete, lasting sometimes but a few moments, or hours, while in other cases symptoms of compression have not appeared until after the lapse of days, weeks, or even several months.

Pearce Bailey (Diseases of Nervous System, p. 100) says: "In the large number of fatal cases the primary unconsciousness is recovered from for a brief interval, if at all." The symptoms usually come on rapidly and death ensues in from twelve to forty-eight hours. The prognosis is better when the symptoms develop slowly. He further says that the length of the lucid interval is usually only a few hours. "It may, however, be protracted for two or three days."

Purves Stewart is reported as saying, "A lucid interval, when followed by the above symptoms (drowsiness, stupidity,

and coma), generally indicates that the hæmorrhage is extradural."

As to the correctness of the latter view we are uncertain. Accumulating experience seems to emphasize the difficulty of distinguishing between the location of hæmorrhage whether extra- or subdural. One thing seems positive, if an opinion may be based upon the twenty-seven cases reported, and that is that long delayed symptoms of cerebral compression indicate positively that the hæmorrhage is subdural.

In the cases reported, in which an interval of two weeks has been arbitrarily selected, every hæmorrhage has been subdural. It might be said, however, that it was found impossible to tabulate cases with entire satisfaction. The symptom selected to indicate hæmorrhage was paralysis. In some cases this was preceded by other symptoms such as headache, dizziness, etc., while in a few no symptoms of paralysis had occurred in the interval of two weeks. In a few almost the first symptom was unconsciousness or a convulsion.

The location of the hæmorrhage is commonly over the lateral surface of the brain. In extradural hæmorrhage, arising most commonly from the anterior branch of the middle meningeal artery, the hæmorrhage corresponds to the distribution of that artery.

In subdural hæmorrhage this is also the most common location, though a clot may develop well down toward the base of the cranial cavity.

The amount of blood varies. In some cases a clot has been found "the size of an almond," while in others clots have been found at operation occupying a considerable part of the cranial cavity, pressing the lateral lobe of the brain downward and toward the median line, a distance of one and a half inches, and flattening the convolutions of the brain.

The exact amount of displacement is difficult to determine, nor is it often possible to measure accurately the amount of blood removed during an operation. It has often been described as four or even six ounces. It is stated, however, that diminution of the cranial contents by one-sixth of its volume is invariably fatal.

The symptoms following hæmorrhage and the order in which they develop seem by no means regular.

After a lucid interval of varying length the patient may in a short time develop symptoms of compression with drowsiness, slow breathing, slow and full pulse, and perhaps convulsions, together with partial or complete paralysis of one or more of the extremities. In cases in which the symptoms develop slowly the first complaint may be of headache, or an indefinite sense of pressure in the head. Dizziness may follow with difficulty in walking. The patient may become somewhat stupid or morose. There may be sudden attacks of vomiting. Finally, the patient may lie in bed in a semicomatose condi-

tion. When roused he may answer questions correctly though slowly and with much apparent effort, and there may be disturbances of sensation, reflexes, etc. Sometimes an arm or a leg may be held in a fixed position, commonly somewhat flexed. The patient may resist efforts to bend or extend the member. This symptom has repeatedly caused errors in diagnosing the location of the hæmorrhage. Since the patient permitted one arm to be placed in any position, but resisted motion with the other, the flaccid arm has been looked upon as paralyzed, indicating hæmorrhage upon the opposite side of the brain. The arm in spastic contraction and simply resisting motion has been regarded as the unaffected one, with uninjured brain center. As a result the skull has been opened upon the wrong side and the offending blood clot has not been found. An observation which may prove of some value in the location of the clot is, that on the contralateral half of the thorax there may be decreased motion in respiration.

The significance of eye symptoms, from observations made thus far, appears to be uncertain. In some cases reported the eyes were seemingly normal. In a few cases blindness has occurred, in other cases the pupil of one side has been dilated, while on the other side the reaction to light has been normal. Hutchinson remarks that irregularity of pupils is rarely present in intra-arachnoid extravasation, and hemiplegia is not so marked as in subcranial extravasation. Phelps (*loc. cit.*, p. 806) states that in those cases in which only one pupil was dilated hæmorrhage was upon the same side in all, but in two cases it was on both sides.

In those cases in which the pupil of one side only has been dilated, this condition is supposed to arise from the pressure of the blood clot on the third nerve of the same side, causing paralysis of the nerve. It has been thought that with injuries to the skull the presence of a dilated pupil, therefore, pointed to a hæmorrhage upon the same side of the skull, but observations show that the symptom does not always permit of this conclusion. Phelps has pointed out (*loc. cit.*, p. 808) that "Dilatation of a single pupil may follow hæmorrhages in other locations than in the middle fossa of the same side as claimed by Hutchinson and may occur in cerebral lesions other than hæmorrhage."

The eyegrounds may show signs of intracranial pressure, but in some cases of hæmorrhage of the brain there has been an absence of any changes in the eyeground. Wiesmann says "In seventy cases of meningeal hæmorrhage, thirty-nine cases showed dilatation of both pupils without reaction. In seven both pupils were contracted. In twenty there was dilatation on the side of extravasation. In four there was dilatation on the opposite side." From our own cases and those presented in the table it is evident that the condition of the pupil and the disk are of very uncertain aid in diagnosis.

Another symptom of cerebral hæmorrhage is increased blood pressure, and it was formerly customary, for its relief, to resort to bleeding. It seems, however, that the increased blood pressure is probably a provision of nature to supply the brain with the blood of which it has been deprived by the pressure of blood accumulated within the skull, thus causing anæmia of the brain itself. It is, therefore, a compensatory effort to overcome anæmia of the brain. When the intracranial pressure has become so great as to overcome the action of the vagus, the blood supply of the brain itself is diminished and death results.

In quite a number of cases among other symptoms has been that of dizziness, and some patients have had sudden attacks of vomiting coming on apparently without any special cause. Constipation is also mentioned as occurring frequently.

Considerable importance in diagnosis should be attached to symptoms of localization in determining the site of the hæmorrhage and the consequent operation. Focal disorders affecting the muscles of the extremities seemed to be uninfluenced by the location of the hæmorrhage, that is, whether the clot is extra or subdural. On the other hand the pressure of a subdural clot at the base of the brain may be indicated by its pressure upon the nerve trunks before their exit from the cranial cavity.

Walton has said that in cases of injury with symptoms developing upon the same side one should be guided as to the point of operation not by the injury to the outside of the skull, but by the location of the injury as pointed out by the localizing symptoms.

In cases in which the development of symptoms has been considerably delayed there may be twitchings of the muscles which receive their nerve supply from the part of the brain compressed by the blood clot. In a number of cases there have been twitchings of the eyelids upon the opposite side. As has already been pointed out, pressure upon the arm or leg center may develop symptoms in the arm or leg on the opposite side of the body. In my own cases these symptoms did not develop for weeks after the injury and when they appeared they came on slowly, that is, there was in the beginning a slight unsteadiness of gait, or slight difficulty in using the hand or arm, or both these symptoms were associated. As time goes on the difficulty may increase until the patient can move the arm or leg only slowly or with very great effort, although the movements of the extremities on the opposite side of the body may be normal. Another striking feature is the slow cerebration of the patient. A patient may be in a somewhat stupid condition, but when roused may answer questions correctly, although slowly, but afterward he will lapse again into a period of stupidity and probably partial unconsciousness. Finally, as the pressure increases, the patient

may remain in a state of unconsciousness with stertorous respiration.

From the symptoms it may be very difficult to determine whether the clot is extradural or subdural. Prescott Hewett states that the middle meningeal artery is the source of intracranial hæmorrhage in nine-tenths of all cases.

Bowen (Guy's Hospital Reports, 1905, p. 2) says that hæmorrhage from rupture of the middle meningeal artery within the skull is usually extradural and is usually associated with fissured fracture of the skull.

Jacobson (Guy's Hospital Reports, 1886, p. 159) states that in 70 cases of meningeal hæmorrhage, fracture was present in 62. Of these 62 cases fracture implicated the base as well as the vault in 38. In 4 there was no fracture. In 3 cases which recovered no fracture was discovered. In 1 there was no evidence whether there was fracture or not.

If the dura is torn, however, the blood will be subdural and Bowen cites 3 cases, one of his own and 2 of Jackson's, as probably of this kind. It seems somewhat doubtful, however, if the source of hæmorrhage in some of the cases reported has been definitely established. Inasmuch as the skull at operation ordinarily is not widely opened, and inasmuch as considerable hæmorrhage may arise from the operation itself, it evidently must be very difficult to determine the origin of the primary hæmorrhage, and it is by no means certain that the reports as to the origin of hæmorrhage are always correct. A very interesting discussion of the sources of intracranial hæmorrhage will be found in an article by Phelps to appear in the May number of the *Annals of Surgery*. His observations are based upon post-mortem examinations, and would seem to strengthen the view that it must often be difficult to determine at operation the exact source of hæmorrhage.

Bowen remarks (*idem*, p. 55): "I venture the opinion, recognizing, however, that the evidence I have put forward is purely negative, that the compressing blood is derived in most cases from the vessels of the pia mater and those running in the subarachnoid space. In a small proportion of cases the blood is derived from the corresponding middle meningeal artery or one of the sinuses of the dura mater."

The rapidity with which the blood may accumulate is a matter of very great uncertainty. It has been suggested that concussion by the disturbance of circulation may for a time hinder hæmorrhage.

Wharton has remarked (*Wounds of the Venous Sinuses of the Brain*, *Annals of Surgery*, 1901, vol. xxxiv, p. 103): "The diagnosis of wounds of sinus of the brain must, therefore, be made largely upon the site of the injury, the character of the blood which escapes, and in cases in which no external wound exists, by the slow development of symptoms of cerebral compression."

	Age.	Sex.
1.	57.	M.
2.	71.	M.
3.	53.	M.
4.	69.	M.
5.	24.	M.
6.	62.	M.
7.		M.
8.		M.
9.		M.
10.	30.	M.
11.	21.	M.
12.	20.	F.
13.	44.	M.
14.	57.	M.
15.	50-60.	M.
16.	63.	M.
17.	23.	M.
18.	60.	M.
19.	29.	M.
20.		M.
21.	26.	M.
22.		
23.		
24.	Adult.	M.
25.	Adult.	M.
26.		
27.	40.	M.

Cystic Clot.—1

While Wharton's conclusions are generally correct it must be remembered that some of the cases in which the symptoms have been unusually long in developing have been hæmorrhages in which the sinuses of the brain were not involved.

The symptoms of hæmorrhage do not seem to enable one to reach any definite conclusion concerning the size of the clot, since in some cases with grave symptoms only small clots have been found. A point in diagnosis has been suggested by Cushing. He remarks that in extradural hæmorrhage from injury of the meningeal artery or venous sinuses the fluid withdrawn by lumbar puncture is clear, while in cerebral or subdural hæmorrhage it is stained with blood. While this point of diagnosis may be of much value immediately following an injury, it is probable that the blood would have disappeared from the spinal canal in cases in which the development of symptoms has been long delayed.

The amount of fluid which has been removed at the time of operation has been variously estimated at from 1 to 6 ounces, but the cases as reported would lead one to believe that the amount of the clot was estimated rather than absolutely measured. In one of my cases it was possible to insert an instrument into the exposed cavity $2\frac{1}{2}$ inches, both anteriorly and posteriorly, from the point of opening, and from the skull to the surface of the brain, a distance of about $1\frac{1}{2}$ inches. It is of course difficult to estimate with accuracy just how large a quantity of fluid such a cavity would contain. Six ounces would not seem to be an overestimate.

The slow development of symptoms has been ascribed to a slowly accumulating hæmorrhage. It is of course possible that blood may for a long time continue to escape from an injured vessel, but it has seemed to me that the slow development of symptoms might better be accounted for as follows: As a result of hæmorrhage a certain amount of blood is poured out. This may not be so great as to prevent the recovery of consciousness and the patient may for a considerable time remain in a seemingly normal condition. Later, the blood clot, acting as a foreign body, may cause the accumulation about it of serum and with this gradual accumulation of serum the symptoms of pressure increase. The primary clot may form definite limitations at its periphery. The later accumulation of serum may find less resistance in compressing the brain than in overcoming the peripheral adhesions and may thus depress the brain.

Two observations have led me to this conclusion. In the first place in my own cases and in some of those cases reported by others, no well-formed blood clot has been found, but a dark-colored fluid containing perhaps particles of clotted blood. On observation of the cavity from which this material has been removed, in some cases thick layers of lymph have been found deposited upon the dura mater. In the second case

which I have reported, the patient was immediately relieved by operation and regained motion and consciousness in a few hours. His condition continued to improve as long as the cigarette drain was employed to keep the opening down to the brain patient. After a few days this cigarette drain was removed, when all of the symptoms of compression returned. Immediately upon opening the wound and carrying a pair of dressing forceps down into the cavity there was a discharge of several ounces of clear fluid. With this discharge all symptoms of pressure again rapidly disappeared but recurred several times when the discharge of serum from the cavity was not perfectly free. It has seemed to me that the fluid collecting at the point of hemorrhage after injury might be similar to that collected at the same place after operation, and just as the symptoms of compression followed the retention of this fluid through the absence or inefficiency of the cigarette drain, in the same manner the pouring out of serum about a clot may cause symptoms of slowly increasing pressure.

In this connection the formation of what are called blood cysts is of interest. Some cases, so described, appear to be those in which the fibrin of the blood has been deposited upon the inner surface of the dura. In reaching the accumulated fluid it has been necessary to perforate a layer which has the appearance of a cyst wall. Below this a dark-colored fluid has been found, but below the fluid could be seen the flattened surface of the brain covered only by the pia. Such a case is No. 27.

Taylor and Ballance, however, describe a cyst with well-formed walls. This was removed entire and measured 7 by $4\frac{1}{2}$ by $1\frac{1}{2}$ inches. In some cases of long standing such cysts have caused absorption of brain tissue. I operated upon one which opened into the lateral ventricle.

It is probable that in some cases clots are liquefied and absorbed. This is indicated by the slow disappearance of symptoms and seems more likely to occur in subdural hemorrhage, on account of the more abundant lymph vessels of the pia. These lymph vessels probably take up the gradually liquefied blood clot.

As to the treatment of cases of hemorrhage there is of course nothing which offers permanent benefit except operation and the removal of the accumulated blood and serum. I do not wish to go into the details of the operation. In as much as the collections of fluid are chiefly in the parietal region, more frequently anteriorly than posteriorly, this is the point at which operation is to be performed, and one may be aided in the localization of the lesion, as has already been said, by the symptoms produced by pressure upon the centers controlling the motion of the extremities and the center of speech. The most common point of hemorrhage, whether it be extradural from the injury of the meningeal artery or whether

it be subdural, is in the anterior parietal region, two fingers' breadth behind the outer side of the orbit and a little below the upper portion of the orbit. This brings one about to the anterior inferior angle of the parietal bone, and it is usually at this point that the bone is crossed by the middle meningeal artery. In some cases the hæmorrhage is from the posterior branches of the meningeal, however, and under such circumstances the hæmorrhage may develop posteriorly and if one has opened the skull anteriorly, failing to find the fluid at the point of operation or in its immediate vicinity, it may be necessary later to open the skull at the posterior portion of the parietal bone. This has been pointed out by Krönlein. The bone flap method is advocated by Krause.

Troublesome hæmorrhage from the middle meningeal may be controlled by placing upon the skull a hemostat, upon the inner jaw of which is a piece of rubber tubing. This will press the artery against the skull and the forceps may be left in situ for a couple of days. The forceps may be included in the dressing and provide good drainage without detriment to the patient. It is important that all clots be thoroughly cleared away, and that strictest asepsis be employed, since otherwise pressure symptoms may not be relieved and the remaining clots before being evacuated may give rise to infection and meningitis.

To reach all clots an opening of considerable size may be necessary. This opening may be closed at a subsequent operation by a bone graft, such as I have fully described in *Boston Med. and Surg. Journal*, April 2, 1906. The method is one I have employed repeatedly and always with success. Later observations have shown that the bone grafts have closed the opening with a solid wall of bone. It seems that such a bony covering must be of value as a protection against accident and by decreasing the possibility of the later development of epilepsy, resulting from the pressure of the cicatrix.

CASE 1. Allen. See text.

CASE 2. Allen. See text.

CASE 3. Armstrong. *Journal American Medical Association*, 1887, vol. viii, p. 679. Male. Age 53 years. Was struck on forehead by brick, February 27, 1887. Unconscious for a short time. April 18, noticed tendency to drag right foot. April 19, fell forward on table suddenly, right arm and leg paralyzed. Examined April 24. Both pupils small and respond to light. April 29, ophthalmoscope showed the optic nerve of the right eye red, border indistinct, veins large and somewhat tortuous. Left eye same. Diagnosis, optic neuritis. Operated May 1. No fracture found. Dura mater dark. No pulsation. On opening dura dark brown fluid blood was found. Patient made good recovery.

CASE 4. Hulke. *Lancet*, 1883, vol. ii, p. 814. Male. Age 69 years. Admitted to hospital October 21, 1881. Received injury of head fourteen days previously. Ecchymosed lump on right temple two fingers' breadth behind angular process of frontal bone just below the temporal ridge. Had been struck a glancing blow on right temple

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by falling ladder. Was stunned for a few minutes, but recovered and went to his work and continued work the remainder of the day. Third day after accident headache was severe and gave up work. On fifth day was lethargic, on following day had retention of urine. Gradually grew more apathetic. On November 1, spastic rigidity of right arm with twitching. Same day trephined at point of injury. No fracture. Dura mater appeared normal. No pulsation. On opening the dura a brown fluid escaped, estimated at from 3 to 4 drams. Day following operation rigidity of arm disappeared. Dressing soaked with turbid brown fluid. Improved gradually. Recovered.

CASE 5. Golding Bird. Guy's Hospital Report, 1901. Report 586. Male. Age 24 years. Injured November 1. Knocked down from behind. Rendered unconscious. Still unconscious when admitted to hospital. Two wounds over vertex and one over occiput. On 4th, complained of severe pain in frontal region. Discharged from hospital November 6. Readmitted to hospital November 16. Had suffered from headache during that period. Previous to readmission to hospital had developed squint and soon became totally blind. Speech difficult. Right arm at times paralytic and at times rigid. Marked aphasia. Operated November 16. Trephined. (From report probably on left side.) Dura mater dark brown color. Dark-colored blood slowly welled up after incising dura mater. November 29 discharged seemingly well.

CASE 6. Harris. Lancet, 1904, vol. i, p. 1199. Male. Age 62 years. June 21 knocked down by stone striking top of head. Stunned short time. Able to walk home. After two weeks partial loss of power in right leg. Later loss of power on left side. No mental symptoms until about a month after accident. Admitted to hospital August 17. Patient talkative and restless. Pupils unequally dilated. Examination of interior of eye unsatisfactory. Left arm wasted, with contracture to angle of about 70°. To straighten arm caused marked pain. Fingers strongly retracted in palm of hand. Both limbs rigid. Left more than right, the left being in a condition of spastic rigidity with adduction. September 5, trephined over right motor area. Dura mater yellow and opaque. Pulsation diminished. On incising, arachnoid bulged upward, appearing dark and somewhat greenish. On incising this a deep claret-colored clot protruded. Altered blood clot and serum poured out, estimated at four ounces. (Question whether the layer of coagulated lymph was not mistaken for arachnoid.) Improved rapidly. On September 11, rigidity of arm and leg returned. On 12th, wound reopened. Clots around the opening removed. September 16, epileptiform convulsions. Clonic spasms in both arms and legs. September 24, paralysis completely disappeared. Mental condition improved. Left hospital November 19.

CASE 7. Keen. American Journal Medical Association, 1901, vol. xxxvii, p. 633. Male. Thrown from street car. Injured over left temple. Scarcely unconscious. Only stunned. Kept in hospital three days and discharged. Six weeks later became duller and finally unconscious. Returned to hospital. Trephined on left side. Vast clot found, extending from frontal to occipital region. Opened posteriorly and a drain passed from anterior to posterior opening. Recovery from operation rapid. Slightly aphasic at time of report.

CASE 8. Kiliani. Annals of Surgery, 1901, vol. xxxiii, p. 325. Male. Injured May 5. Struck in left parietal region by a brick. Did not become unconscious, but was dazed for a short time. May 20, did not use right hand well. May 22, violent frontal headache. May 26, dizzy and almost fell. June 1, slight hesitancy in speech. Increased up to time of admission to hospital on June 6. June 7, took little notice of surroundings and was somnolent. Slight spastic paresis of right arm and hand, less in right leg. Ataxia in both arms. Partial

motor aphasia. Ophthalmoscopic examination showed nothing abnormal. Pulse 60 to 94. Respiration 12 to 24. June 11, operated on left side over injury. Dura tense, non-pulsating, dark color. Clot covering practically the entire left hemisphere evacuated. Recovery rapid. August 19, patient perfectly well and attending to business.

CASE 9. Kamerer. *Annals of Surgery*, 1901, vol. xxxiii, p. 325. Male. Fell from bicycle. Unconscious for short time. (Estimated variously from one-quarter to three hours.) At end of ten days felt perfectly well. Six weeks after accident began to complain of headache. Symptoms increased in severity for two weeks. Trephined. Large amount of dark fluid and much clotted blood found behind dura. Blood clot was about $\frac{1}{4}$ inch thick; lying upon brain and above this was the colored fluid. Brain separated from skull about $1\frac{1}{2}$ inches. Patient recovered. Free from symptoms for a considerable time. Six months later second operation. Patient died in about a year.

CASE 10. Dawbarn. *Annals of Surgery*, 1907, vol. xlv, p. 161. Male. Age 30 years. Seen on November 21, 1905, twelve days after receiving a severe blow from a club on right side of head. History unsatisfactory, except that patient complained much of headache after injury and seemed increasingly stupid. Had been entirely unconscious during three days previous to admission. Both eyes directed sharply to right. Pupils equal and of normal size. Evidence of but one wound on right over Rolandic fissure. Linear undepressed fracture distinguishable. Thick blood clot exposed. Clot extended well down to base of brain. Considerable hæmorrhage from fracture down toward base controlled by packing. After this operation no recurrence of left side convulsions. Patient became partly unconscious and eyes no longer turned to right. Forty-eight hours later, severe chronic convulsions of entire right side. Operated second time. Operation over left Rolandic area of skull. Dura bulged strongly into the opening. No pulsation. On opening dura an extensive partly organized clot was found. Rapid recovery.

CASE 11. Carson. *American Journal of Medical Science*, vol. ciii, 1902, p. 134. Male. Age 21 years. Injured by fall. A week later suddenly became unconscious. Shortly afterward had difficulty in speaking. First seen 13 days after injury. For the three days preceding this had been unable to speak. Pulse down to 54. Patient seemed to understand what was said to him. Left nasolabial fold more marked than right. Right cheek puffs on attempting to whistle. Tongue diverges to right. Grip of both hands about equal. No difference noted between right and left legs and arms. Seemed to be able to write figures, but not letters. Day later grip of right hand seemed to be less than that of left. Operated April 29, 1891. Left side, $1\frac{1}{4}$ inches behind the external angular process. Dura dark and cloudy. No pulsation. On opening the dura clot found extending in all directions. On raising dura a stream of dark semi-liquid blood forced itself through the supervening layer of clot, being projected a distance of three feet. Thickest part of clot immediately under anterior branch of middle meningeal artery. Recovery rapid. Dismissed May 18. October 15, 1901, patient in good health, working in a brickyard.

CASE 12. Hamilton. *Journal American Medical Association*, 1894, vol. xxiii, p. 952. Female. Age 20. Struck on right side of head just posterior to Rolandic fissure on June 18, 1893. No record concerning unconsciousness. Severe headache. Gradually lost sight in right eye, becoming totally blind. Deafness began almost immediately in right ear. No motor paralysis. Vision and hearing normal on left side. Ophthalmoscope shows O. S. normal. O. D. slightly vascular. No evidence of past or present neuritis. Operated November 15. Dura mater normal. Incised dura. Passed silver wire loop down to optic

commissure. On withdrawal of wire a firm, round, coagulum body, 3 cm. in length followed the wire. This was repeated a second time. Patient rallied well from the operation. On second day had convulsions with total loss of consciousness and spasmodic contractions of left arm and hand. Wound reopened. Other coagula were removed. November 18, patient re-examined and in good health.

CASE 13. Stewart. *British Medical Journal*, 1887, vol. 1, p. 877. Male. Age 44 years. Admitted to hospital February 22, 1887. On first of January had fallen on back of head. Lost consciousness for a minute or two. Remained well for a fortnight when he began to have pain with severe headache. Week later pain was so severe that patient was unfitted for work. His legs were feeble and his walk was unsteady and staggering. Head showed no marks of injury. Movements of eyes and eyelids were normal. Right pupil slightly larger than left. Both pupils reacted and were normal. Ophthalmoscope showed optic neuritis of both sides. No loss of power in any individual muscle or group of muscles. On February 26, gait was unsteady, tendency to vomit, increasing stupidity and torpor. Tapping over triceps and biceps induced movement on right side, but none on left. February 28, condition approached one of coma. Right arm and leg distinctly paralyzed. Aphasia well marked. March 1, symptoms being still more pronounced, was trephined over posterior part of third left frontal convolution. On opening the dura a quantity of serous fluid escaped, reddish brown in color and afterward dark red. Amount estimated to be about 6 ounces. The fluid extended forward two inches and backward about three inches. Copious discharge of serum for two days. Patient's condition very satisfactory. On March 3, rise in temperature, slight rigor, nausea and vomiting. Symptoms gradually grew worse, passing into coma, with complete paralysis of right side. Patient died at 11 o'clock on March 6. The details of the case render it strongly probable that death was from sepsis.

CASE 14. Burns. *Lancet and Clinic*, 1907, vol. xcvi, p. 82. Male. Age 57. On October 27, 1905, was struck on the malar process and was unconscious ten to fifteen minutes. After twenty minutes sat up and was able to answer questions. Normal pulse. No evidence of fracture, concussion or compression. Returned to work ten days after injury without complaining of headache. January 7, patient talked in a normal manner and his gait and reflexes were apparently normal. He was advised to enter hospital for observation, but declined to do so. Entered hospital on January 25. Operated January 26, history showing that few days after being seen on January 7, he had fallen into a stupor and exhibited signs of hemiplegia. At this time he had left-sided paresis, extending to the face and tongue. There was evidence of pressure over the leg, arm, orofacial and tongue areas. Marked mental hebetude. Pulse 62, temperature 98. Operated over the motor area on the right side. The dura bulged into the opening, was bluish in color and without pulsation. On incising the dura an old clot of large size spread out in all directions. Patient recovered rapidly and on the third day was able to hold a glass of milk in his left hand and flex and extend the left arm normally. The functions of the muscles of the face and tongue were restored. Patient died, however, on February 2. Death was ascribed to pressure causing cortical atrophy, followed by degeneration of the lateral columns of the spinal cord. The published account gives no history of post-mortem or microscopic examination.

CASE 15. Hume. *Lancet*, September 19, 1908, p. 866. Male. Age 50 to 60 years. On August 9, 1907, fell, striking on back of head on left side. Unconscious for a few minutes. Wound healed rapidly. Felt vaguely ill afterward. During September was much depressed. By October 1, began to lose power in right hand and walked

with difficulty. On October 29, broke down and could no longer sign name. Retained some memory up to November 14. Examined by Dr. Hume, November 1. Patient had vomited suddenly several times. Distinct loss of power in right hand. Less distinct paresis of left leg. By November 7 all symptoms had increased. Spoke with difficulty, had right facial paralysis, several times had involuntary defecation and micturition. Absence of knee jerk, ankle clonus and patella reflexes. Optic discs congested and edges blurred. November 14, cranium opened on left side in posterior parietal region. Dura mater bulged outward and was bluish in color. When incised 5 to 6 ounces of porter-like fluid escaped. Some clots adherent to dura, but not to brain surface. Surface of the brain was depressed, but rose gradually to normal level. Gauze drain inserted. Bone not replaced. Same evening patient could answer ordinary questions correctly. He could move right leg and to a slight degree extend right arm. Patient gradually improved, regained perfect speech, and the full use of both arm and leg, and returned to his usual occupation.

CASE 16. Bartlett. *Hahnemannian Monthly*, vol. xxxviii, 1903, p. 741. Male. Age 63 years. In June, 1902, received a blow upon the head which caused him to remain sitting for a half hour. There was a wound to the right of the median line over the anterior portion of the parietal bone. That such an injury had occurred had been forgotten until the time of operation, which occurred in the latter part of March, 1904. In December the patient had developed vertigo. Early in February he developed severe headaches. In the middle of March he showed marked drowsiness and by the 25th of the month this had increased so that it was difficult to rouse the patient. An examination this time showed that the left knee jerk was more energetic than the right. The patient could be roused sufficiently to protrude the tongue. He did this in the median line. A dynamometer grasped in the right hand registered 40 and in the left 15. Pupils moderately contracted and equal. Ophthalmoscopic examination unsatisfactory. Patient was trephined just above the hair line and one inch from the median line on the right side. The dura was unduly tense. On incision there was a forcible gush of reddish serum, about 1 to 2 ounces escaping. Brain was depressed and in the bottom of the cavity was some old blood clot. Wound packed with gauze. Following morning patient was perfectly conscious and headache was gone. On the 27th patient was again drowsy, but on removal of packing he improved. Several days later Jacksonian epilepsy developed with convulsions beginning in the left hand and extending to face and left leg. Convulsions were followed by paralysis of left hand. Patient never lost consciousness. Convulsions gradually decreased and disappeared after three or four days. Patient improved. Reported to the doctor's office May 3 and again on September 8 as entirely well.

CASE 17. Wells. *Medical Record*, vol. xli, May, 1892, p. 541. Male. Age 23 years. Was seen to fall suddenly in the street and went immediately into convulsions. He frothed at the mouth and his face became cyanosed. No history of case could be obtained and no evidence of injury except a small scar on the left side of the head anterior to and a little above the ear. This was judged to be three to six weeks old. Both pupils dilated and equal. Reflexes appeared to be normal. Temperature 102, respiration 30, pulse 120. No apparent loss of motion or sensation. During evening temperature rose to 104 and patient became delirious. August 22, the record shows that during previous night convulsions were nearly constant and patient, who had been in hospital two days, was rapidly failing. Diagnosis, cerebral abscess from an old injury. Skull was trephined August 23, at the location of the scar. At time of operation temperature was 105, pulse 123, respiration 22. No evidence of fracture. The dura was dark

in color and presented no pulsation. On incising dura blood clot immediately protruded and a handful of blood clot was removed. The clot extended along the fissure of Rolando covering the motor areas of the face, arm and leg. Pia appeared to be much reddened and inflamed and the brain was depressed. Opening was drained by gauze and a tube. August 24 and 25 patient had several convulsions. On August 25 temperature fell to 99 and continued at about that level until recovery. Discharge from wound greatly lessened. Patient regained his memory and stated that three weeks before admission to hospital he was struck upon the head. Injury had, however, caused him no trouble. For a week previous to admission to hospital he remembered that he had had headaches, and for a few days had noticed that his right arm and leg were not as strong as usual, but the difficulty was not sufficient to cause him to stop work. On September 23 patient was dismissed cured.

CASE 18. Hahn. *Deutsche Medicinische Wochenschrift*, 1896, April 16, p. 250. Male. Age 69 years. Admitted to hospital August 19, 1894. Six weeks previously had been struck in the right parietal region. Since that time patient had not felt well. Headache on right side, fretful and easily angered. During past six days marked change in condition. Gradual weakening of left arm and leg and patient has remained in bed and been apathetic. For last two days has been unconscious. Occasionally he was very restless, grasping at the right side of head. No convulsions or vomiting. Patient answered questions only when thoroughly roused. Facial nerve of left side showed slight paresis. Left arm showed slight spastic contraction and was paralyzed. Left leg paralyzed, left hypoglossal and other cerebral nerves not involved. Pupils equal and react to light. Eye grounds normal. Eye muscles seemingly intact. Sight seemingly normal. Sensibility seems dull, but the same on both sides. Patella reflexes increased. Patient gradually went into a state of deep coma. Operation at point of injury, a little above right ear. No evidence of bone injury. Dura mater was tense and bluish in color. No pulsation. On opening dura nearly 150 c. c. of clotted blood was evacuated. Cavity lightly packed with iodoform gauze. On August 11, patient's mind was clear. Spastic paralysis of left arm had disappeared and patient could move right arm and leg. Paresis of face had disappeared. August 13, no fever, patient slept well. Had good appetite. Good grip in left hand. September 7 in excellent condition. October 10, patient dismissed in seemingly normal condition.

CASE 19. Korte. *Deutsche Medicinische Wochenschrift*, 1903, p. 118, No. 7. Male. Age 29 years. Entered hospital November 30, 1901, in unconscious condition. Four weeks before he had received a blow upon the head. He was momentarily unconscious. He recovered completely and worked until the day before admission to hospital. Last evening ate supper as usual and went to bed. Suddenly in the night had a convulsion and lost consciousness. Temperature normal. Pupil reflex. Patella reflexes. Sensibility and motion of extremities normal. No anomalies in the cerebral nerves. No paralysis. Patient slept most of time. Did not respond intelligently to questions. A scar was found over the right parietal bone, being adherent to the skull. December 1, typical epileptiform attack. December 2, epileptiform attacks had gradually increased and were followed by unconsciousness. In the afternoon the attacks recurred about once in two hours. Patient would throw himself upon right side. There were convulsive movements first of the left arm and then of the right. Attacks lasted about two minutes. Patient became wholly unconscious. December 4, trephined at site of scar. Dura mater tense. No pulsation. Nothing pathological between bone and dura, no injury to bone. On opening dura marked injection of the superficial vessels of the

brain. A puncture of the brain in various directions showed nothing. Dressing applied. Patient died on December 6. At post-mortem examination in addition to other conditions there was found in the left frontal lobe, principally under the first orbital convolution, a point of softening the size of a walnut. The softening of the brain substance had evidently been caused by the dark red blood clot which was found at this point.

CASE 20. Duret. *Semaine méd. Par.*, vol. ii, p. 119, 1891. Butcher was thrown from wagon to the ground; he was able to get back to his feet and continue his pursuit, but suffered pain in left parieto-occipital region. On 15th day headache became very intense and produced a complete aphasia. Consciousness not impaired. Motor aphasia complete. Trepanation revealed a clot beneath the dura mater. Removed about two teaspoonfuls of blackish fluid. Could say yes and no on fourth day, continued to improve, dismissed entirely restored. Unfortunately on 23d day, after copious libations, he was attacked with severe cerebral congestion and died in convulsions.

CASE 21. Starr. *Brain Surgery*, p. 107. Patient, age 26, since injured with penknife unable to find words. After fourteen days disturbance of speech increases, and the pains in wound increase. Trepanation. Knife had penetrated dura and brain; dural wound was enlarged and black blood detritus removed. Rapid improvement. Complete recovery.

CASE 22. Hulke. *Seydl. Antisept. und Trepanat.*, p. 48. Case of trauma; transitory unconsciousness; worked for two days. During course of fourteen days dizziness and impaired speech developed; a few days later unconsciousness and paralysis of right extremities, abolition of reflexes; in a few days more spastic rigidity and convulsions of left arm. Trepanation. Incision on right side; discharge of brownish red fluid; one hour later consciousness returned. Went back to work in eight weeks. Case of collateral hemiplegia with operation on same side.

CASE 23. Ceci. 1887. *Schædeltrepanation bei Hemiplegie und Koma. Deutsche Med. Ztg.*, vol. ix, No. 40, p. 459. Injury to right upper parietal region. Paraplegia followed two months later, and then complete left-sided hemiplegia; deviation of tongue to right side ten days later, disturbance of speech, involuntary micturition, coma. Probable diagnosis, cerebral abscess. Trepanation. Revealed free extravasate of blood under dura mater; puncture of brain substance failed to reveal abscess. Gradual complete recovery.

CASE 24. Fletcher. 1896. *Peoria Medical Record*, vol. i, p. 248. Patient fell seven feet, striking back of head, unconscious for one hour, slight bruise over center of occipito-parietal suture of left side. Recovered sufficiently to eat his breakfast and go to work. Had some delusions of sight, which increased, until he gave up his situation and retired to his farm. In six months memory greatly impaired as to locality; visual delusions, stupor, coma, with respirations at five per minute and indications of immediate death. Trephined over seat of injury, dura bulging through the opening, divided the dura, about one ounce of bloody serum escaped, followed by immediate relief, respirations, pulse and temperature becoming normal. The patient sat up next day and has continued in good health since, now four years.

CASE 25. Guerry. 1906. *Jour. South Carolina Medical Association*, vol. ii, p. 328. Patient was struck with knife blade over the left Rolandic fissure. Blade removed at once and no symptoms beyond a transient hebetude. Went to work next day. Twenty-one days after receipt of injury he noticed that he was losing use of right arm and

Allen: Intracranial Hæmorrhage of Traumatic Origin

leg; four days later profound coma; pulse 40, temperature 98, respirations 10, with complete paralysis of right half of body. At operation a large subdural clot was found over left Rolandic fissure. Recovery slow.

CASE 26. Dawbarn, in discussing Kiliani's paper, Case 8, referred to a case which received a blow on the right side of the head. The following week the patient became somewhat irritable. Later he developed a partial left hemiplegia and left facial paralysis. Patient continually placed hand over right side of head to indicate where struck. Trephined on right side, but nothing was found. Patient died two days later. Autopsy revealed large blood clot over left motor area on side paralyzed, between the dura and the skull. Hæmorrhage was apparently the result of contrecoup. The brain and medulla were submitted to Dr. Gray, who reported it was one of the rare cases where the motor fibers had not crossed, but gone down straight, each on its own side of the medulla and cord.

CASE 27. Boyd. Clinical Societies Transactions, London, vol. xxv, p. 157. Male. Age 40 years. Fell from horse March 31, 1901. Stunned and carried home in a cart. On reaching home, twenty minutes later, was conscious and walked upstairs. Diffuse swelling over left side of head and forehead. Was kept in bed for a fortnight, complaining chiefly of headache. Returned to business April 21. On June 18, his headache returned and he noticed difficulty in writing and could not carve or button his coat. With his eyes closed he was inclined to walk to the right. From time of injury had loss of sense of smell. On June 22 the patient was confused and dull. No tender spots on head. The movements of the right arm could be performed but were weak. Tactile sense normal. Walked fairly but could not go upstairs well with right leg. Increased knee jerk on right side. Sight good. Disc normal. Pupil symmetrical, react to light and accommodation. Cranial nerves normal. June 25, right arm almost completely paralyzed. Right leg weak. Some rigidity of right arm and leg. Right eye congested, pupil contracted, and lid drops. Patient now had pain over left parietal region, increased by pressure. By June 28, patient had become comatose and the leg was completely paralyzed. Trephined on the left side over the middle of the fissure of Rolando. There was a possible linear fracture, but this was uncertain. Dura bulged markedly. No pulsation. On incising dura a grayish yellow surface was exposed. It was supposed to be the brain surface with pus beneath it. On incising this 4 ounces of dark red clear fluid escaped. (The collection was called a cystic clot. It seems probable that a layer of plastic lymph had been incised instead of the brain surface.) A drainage tube was placed in the cavity. At 11 p. m., patient said, "Good evening, Doctor," and immediately became again unconscious. During the night he roused up and talked incessantly. June 29 patient improved. Could move both arms and legs. By July 8 patient said he felt well. He was up July 29. On August 15 was seen by doctor. On August 27 he seemed to be entirely recovered.

BLOOD CYST.

CASE 28. Taylor and Ballance. London Lancet, 1903, vol. ii, p. 597. Male. Age 34 years. In February, 1902, fell, striking right side of head against a stone. He returned home and was unable to work that day. Some three months after patient suffered from headache. Headaches gradually grew worse and by July 10 patient had difficulty in walking and was becoming dull mentally. At this time there was marked weakness in left arm and leg. Pain continued in head. At this time some blurring in right optic disc was noticed. Admitted to hospital and remained a month. At that time was considered insane. Returned in August and the presence of optic neuritis led to a diagnosis of tumor

of brain, the variable character of the paralysis of the left arm suggesting a fluid tumor, possibly an abscess. He was admitted to hospital August 20, 1902. His general health was much deteriorated, loss of memory for recent events, and gait irregular and swaying. Deep reflexes were exaggerated on the left side. Optic neuritis with retinal hæmorrhage existed on the right side. Headaches were intermittent. Diagnosis, cerebral tumor in the right frontal region. Operations were in three stages, September 1, September 6 and September 18. At the latter operation there was a temporary ligature of the internal carotid artery. A bone flap $5\frac{1}{2}$ inches anteroposteriorly by $4\frac{1}{4}$ inches vertically which had previously been made was turned back. A cystic tumor lying behind the dura but not adherent to the brain was removed. It was not connected with any main vessels. The cyst on removal measured 7 inches in length, $4\frac{1}{2}$ from above downward, and $1\frac{1}{2}$ in thickness. The bone flap was replaced and sutured. The patient was discharged January 15, 1902. He seemed to be in perfect health on May 26.

Calcification of Fibromyomata of the Uterus.

By IRVING LUDLOW, M. D., Cleveland.

(From the Department of Surgical Pathology, Western Reserve University.)

Extensive calcification of fibromyomata of the uterus seems to be of sufficient infrequency to merit the report of the following case which occurred in the service of Dr G. W. Crile, through whose courtesy it is presented.

The patient, aged 53, single, was admitted to Lakeside Hospital Aug. 24, 1905. The family history had no bearing on the case.

Previous History: Patient had scarlet fever at six years of age, typhoid fever at 10 years and acute rheumatism at 30 years. Menses were always regular and normal in amount and duration. Patient was never very strong during the period of middle life.

Present Trouble: Two years ago (1903) she first noticed a tumor mass in the lower abdomen. It slowly increased in size, the growth being accompanied by some pain in the back and constipation, but no other symptoms.

Operation: On Aug. 25, 1905, an abdominal hysterectomy was performed. The patient made an uneventful recovery.

Pathological Report: The specimen (Fig. 1) consists of the uterus and tumor, weighing together, 900 grammes. The upper portion, comprising four-fifths of the entire mass, measures 14 x 10 x 7 cm. It is very nodular and feels like a calcified mass. The nodules are of varying size and are white in color. The anterior surface is more nodular than the posterior, the peritoneal covering being very adherent to the nodules. The lower portion, consisting of the uterus and smaller nodules, measures 6 x 6 x 6 cm. At its upper border are the tubal openings. This portion is also nodular but not so hard as the upper part. The peritoneal covering is also less adherent. The external os can be seen slightly posteriorly. A cross section of the tumor, made with a saw, presents white, irregular areas of calcification, which, with the included soft tissue, forms a coral like structure (Fig. 2).

Read before the Clinical and Pathological Section of the Academy of Medicine of Cleveland, June 4, 1909.

Microscopic Examination: A section from the soft portion of the tumor mass is composed of fibrous and muscular tissue, irregularly distributed. In some portions the fibrous tissue predominates, while in other places the muscle is in excess. For the most part the tissue stains well, but certain parts show varying degrees of hyaline degeneration. The blood supply is very deficient.

In a section from the hard portion of the tumor no distinct muscle fibers can be seen, these probably having undergone fibrous change and then hyaline degeneration. There are a few faintly staining connective tissue fibers, but for the most part this tissue has also undergone hyaline change and necrosis. Here and there throughout the section are irregular areas, which stain a diffuse bluish-violet color with hematoxylin, the areas of calcification. No blood-vessels can be recognized and no bony structure is found in the section.

Chemical Report: Dr H. D. Haskins examined a portion of the calcareous mass, chemically, and found that the ash amounted to 32% of the weight of the moist tissue. Qualitative testing of the ash showed a large quantity of calcium phosphate and a little calcium carbonate with a very slight trace of magnesium. This agrees with Wells¹, who states that the composition of the inorganic salts in calcified areas in the body seems to be practically the same, if not identical, whether the salts are laid down under normal conditions (ossification) or under pathologic conditions, viz.:

	Mag. phosp.	Calc. carb.	Calc. phosp.
Pathologic calcification (Human tuberculosis)	1.2	10.1	87.8
Normal ossification (Human bone). 1.57		10.1	87.4

Report of X-Ray Findings: The shadow made by a thin section of the calcified tumor was very dense (Fig. 3), while with rays of the same penetrating power, bones of the finger, taken for comparison, showed only a slight shadow. No bony structure could be observed in the section submitted to the X-ray examination. My thanks are due to Prof. Harry Hower, of the Carnegie Institute, Pittsburg, Pa., for the X-ray plate.

A review of the writings upon this subject from the time of Hippocrates is given by Everett² who found only 51 cases mentioned; and of these it is questionable whether 18 of them are not reproduced with alterations, leaving only 33 well authenticated cases.

The earlier cases were simply reported as uterine stones, thus Hippocrates relates the case of a Thessalian maid of 60 summers, who during her younger years suffered great pain during intercourse. No complete history of the case is given but we learn that the patient, after having partaken freely of leeks, was seized with intense uterine pains, after which she was delivered of a rough stone the size of a child's head.

Louis³ in 1753 had collected 18 cases. Velpeau reported three cases. De Coze removed a calcified fibroid with obstetric forceps, the operation being followed by fatal hemorrhage. Säxinger⁴ found a stone the size of a child's head which, with much difficulty, he seized with forceps and delivered, producing extensive lacerations which resulted in peritonitis and death.

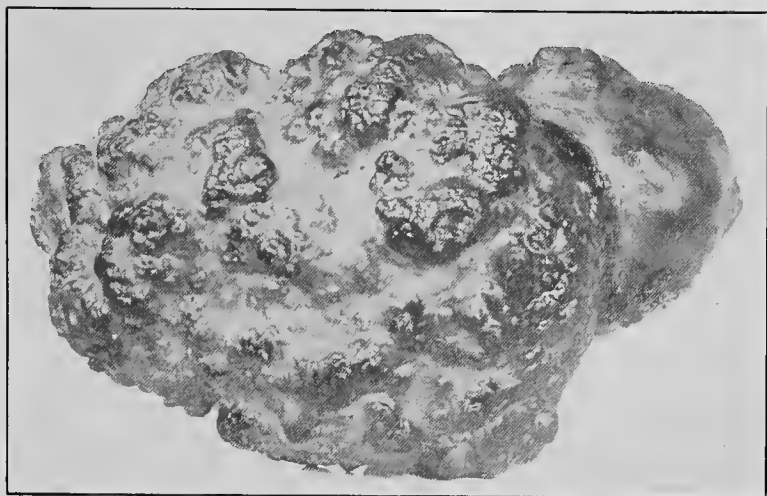


FIG. 1

Böhm of Gunzenhausen, obtained a calcified fibroid weighing five kilograms, from the body of a nulliparous woman, who had died of marasmus. This tumor was encapsulated in the left abdominal region; it measured 13 inches in its longer and eight inches in its shorter diameter. The texture was so dense and compact as to be susceptible of a high polish. It was of a pure calcareous nature, the organic tissue having been entirely absorbed. Its external portion was not so dense as the center. It had encroached upon the bladder to such an extent that it caused the deposit of a calculus in that viscus.

E. E. Montgomery,⁵ in 1880, reported a case of multiple uterine fibroids partially calcified. Since that time cases have been reported by Potter,⁶ Upshur,⁷ Wright,⁸ Baer,⁹ Cushing¹⁰ Edebohlis,¹¹ Cavaillon,¹² Mouchet,¹³ Withrow,¹⁴ and Hallopeau.¹⁵

Tracey¹⁶ made a study of the degenerative complications and associated conditions in 3516 cases of fibromyomata of the uterus. He found that about 35% had undergone some form of degeneration. Calcareous changes were found in 123 cases or 3.4%; although no report is made upon the extent of the process this number doubtless included all degrees of degeneration. An examination of the Lakeside Hospital pathologic material and records of 210 cases of fibromyomata of the uterus shows three cases of calcification. In one case there was a single, completely calcified, submucous mass about three cm. in diameter, the second



FIG. 2

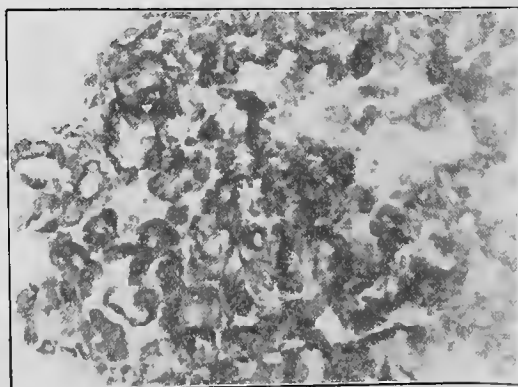


FIG. 3

showed a few small isolated areas of calcification and the third is the case reported in this paper.

In analyzing the etiologic factors of calcification we must consider the following: (1) The calcium salts must come from the blood, where they are held in solution or in suspension by the proteids, either as the carbonate and phosphate, or as calcium-ion-proteid compounds or perhaps both. This suspension, or solution, is in an unstable condition possibly only because of the extremely small portion of calcium in the blood (about 1:10,000) which renders it liable to be overthrown. (2) There must be retrogressive changes in the tissues. Calcification never occurs in normal tissue except in the formation of bone. Fibromyomata may undergo hyaline, fatty or waxy degeneration, all of which are favorable to the deposit of lime salts, as is also necrosis, especially when absorption is deficient. Most investigators favor the theory of the formation within the degenerated area of certain substances as phosphoric acid, fatty acids and certain proteids which have a special affinity for calcium. When this calcification occurs in local areas, e. g. in the submucous fibroid, we have formed the so-called womb stones. In some cases the deposit commences in the center of the tumor and extends outward, more rarely in the external layers so as to form a shell around the tumor. On account of interference with nutrition, calcification of one portion of a tumor may be accompanied by suppuration in other portions. Finally the process may be so extensive that the tumor can be cut with a saw and the cut surface polished, more usually, however, it is incomplete and forms a coral-like skeleton.

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A SIMPLE METHOD OF ESTIMATING THE COMMON VARIATIONS AND DEFORMITIES OF THE FOOT.¹

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PRESENT METHODS OF STUDYING THE FOOT. There is no part of the human body so subject to deformities as the foot, yet there is no part of the body of which the estimation of deformities is so inaccurate and vague. The most common deformity that we see is flat foot, yet the diagnosis of flat foot, so far as its physical signs go, rests on the most ambiguous basis, and in attempting to teach students what we mean by the term, we seldom are able to present a convincing and definite picture. The only method which pretends to any accuracy at all is that of taking a print of the bottom of the foot. The deductions thus made are dependent on the extent with which the sole of the foot touches the underlying surface. Then the shape of the print is supposed to be an index of the lowering of the arch. I see little value in this method. In the first place, the print of the foot only represents the imprint of the skin of the sole. If a foot happens to be fleshy or swollen, it naturally makes a broader impression, and thus seems to connote a lower arch than when a foot is thin and not swollen. Again, a foot which may be very flat may make an almost perfect print, so called, if its arch has not been lowered quite enough to be represented properly in the print. But even if one admits that this method does aid in diagnosis in extreme types of the disorder, it adds nothing in estimating the amount of lowering of the arch in those types which are intermediate. Therefore, in the last few years I have sought for a more definite basis for comprehending certain deviations, with special reference to the estimation of the height of the arch; the aim of this paper is to suggest such a method.

THE ESTIMATION OF THE DEFORMITY IN GENERAL. In examining the malformations of the body there is no process more valuable than that of studying the relationship of bony landmarks to one another. In fractures of the wrist and of the ankle the relationships of the ends of the long bones are of extreme importance. A splendid example of valuable relationships is Nélaton's line. I may further call attention to such important methods as Bryant's triangle and Meyer's line. These simple geometric methods can hardly be omitted for a clear and proper elucidation of the deformity.

THE SELECTION OF BONY LANDMARKS OF THE FOOT. In the case of the foot no such method has ever been advanced, so far as I know,

¹ This paper represents the substance of a monograph which the author is preparing, in which the work will be presented in greater detail.

and with this in mind I have selected certain landmarks for study. The ones chosen are the lower posterior corner of the internal malleolus, the tubercle of the scaphoid bone, and the lower tubercle on the head of the first metatarsal. The reason for selecting these particular landmarks will be more evident as we proceed. Before advancing, let me briefly examine these landmarks, as it is absolutely essential that the observer know definitely just what part of the skeleton his finger touches in the examination. Fig. 1 is a wash drawing of a disarticulated skeleton which brings into exaggerated relief the landmarks in question.

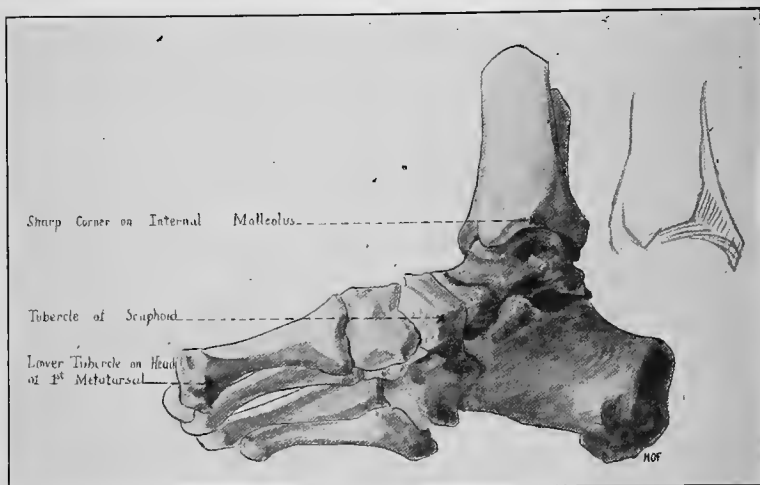


FIG. 1.—The position of the bony landmarks under consideration.

The Lower Tubercle of the Head of the First Metatarsal Bone. In examining the head of the first metatarsal bone in the disarticulated skeleton, we find on its inner aspect two ridges separated by a groove. Each of these ridges ends posteriorly in a prominent tubercle. The upper tubercle does not concern us; the lower one is sharp, and is the one which applies to the present series of observations.

The tubercle of the scaphoid bone is best seen by looking at the scaphoid bone from above. It will then be apparent that the whole internal surface of this bone forms a ridge. The apex of this ridge is the so-called tubercle, being, in fact, the most prominent bone palpable. The tendon of the tibialis posticus ends close to this tubercle.

The Posterior Inferior Corner of the Internal Malleolus. As seen in the sketch, and as will be apparent on examining the skeleton, the internal surface of the tibia is bounded at its lower end (internal malleolus) by three edges—an anterior, an inferior, and a posterior edge. Where the posterior edge strikes the inferior edge a sharp

corner can always be felt. If we run our finger over the part in question we simply determine the most inferior posterior corner of the internal malleolus as thus evidenced.

CHANGES IN THE SKELETON OF THE FOOT WITH WEIGHT-BEARING. The investigation of the foot differs from that of the other parts of the body in one respect—that the relationship of the bones becomes altered with weight-bearing. Their alteration is necessarily the first study which most concerns us. As similar studies have been made by other observers, I shall confine myself to the change in the relationship of the landmarks in question.

According to the literature,² the view seems pretty well established that when weight is borne the scaphoid travels downward and inward. The downward displacement is, for our purpose, the important thing. In the study of six living feet which I radiographed, with and without weight-bearing, I marked the posterior inferior corners of the tibia, the head of the first metatarsal, and the scaphoid. (The external landmarks selected cannot be accurately identified in the Röntgen pictures.) I then drew a connecting line between the point marked on the internal malleolus and that on the head of the first metatarsal. Figs. 2 and 3 illustrate one of these cases and show that in weight-bearing the scaphoid becomes distinctly depressed with respect to the connecting line. However, as these points on the Röntgen pictures do not exactly correspond to the external landmarks which I selected (earlier described), I marked these landmarks with and without weight-bearing and photographed the feet (Figs. 4 and 5). These pictures point to a similar but more practical conclusion, that in weight-bearing the scaphoid becomes depressed with respect to the line connecting the lower posterior corner of the internal malleolus with the lower tubercle on the head of the first metatarsal.

It is, therefore, evident that in selecting the scaphoid bone, I have taken a part of the foot very susceptible to change in weight-bearing, and on a basis of the above observations and others,³ not described in this report, I may state that the weight-bearing foot differs from the non-weight-bearing foot according to a definite rule. This rule is that in weight-bearing the scaphoid descends, as measured from the base line as established above.

THE STUDY OF THE POSITION OF THE SCAPHOID TUBERCLE IN ONE HUNDRED YOUNG MALE ADULTS. After having studied the anatomical data above described, I examined a number of apparently

² G. H. V. Meyer, *Statik und Mechanik des menschlichen Knöchelgerüsts*, 1873, and *Statik und Mechanik des menschlichen Fusses*, 1886; John Dane, *Trans. Amer. Orth. Assoc.*, 1897; Golobiewski, *Ztschr. f. orth. Chir.*, 1894; Lovett and Cotton, *Trans. Amer. Orth. Assoc.*, vol. xi; Bradford and Lovett, *Text-book of Orth. Surg.*, second and third Editions; Whitman, *Orthopedic Surgery*; and Quain's *Anatomy*.

³ In the monograph another method of measuring the excursion of the scaphoid in weight-bearing is described. This consists in using the angle which it forms with the vertical dropped from the internal malleolus. The results so obtained confirm the main observation.

healthy individuals with reference to these points. The individuals chosen for the observation were young male adults from the evening



FIG. 2.—Röntgen picture of a foot without weight-bearing: *c*, marks the posterior inferior corner of the head of the first metatarsal; *a*, the posterior inferior corner of the internal malleolus, and *b*, the posterior inferior corner of the scaphoid. A vertical line is erected from *b* to *a-c*.



FIG. 3.—Röntgen picture of the same foot as in Fig. 2 with weight-bearing. The same points are marked. Note the increased distance of *b* from the connecting line.

gymnastic class of the Cleveland Young Men's Christian Association. The men were taken as they came along, and no questions were asked. It may be assumed that such a gymnasium would furnish

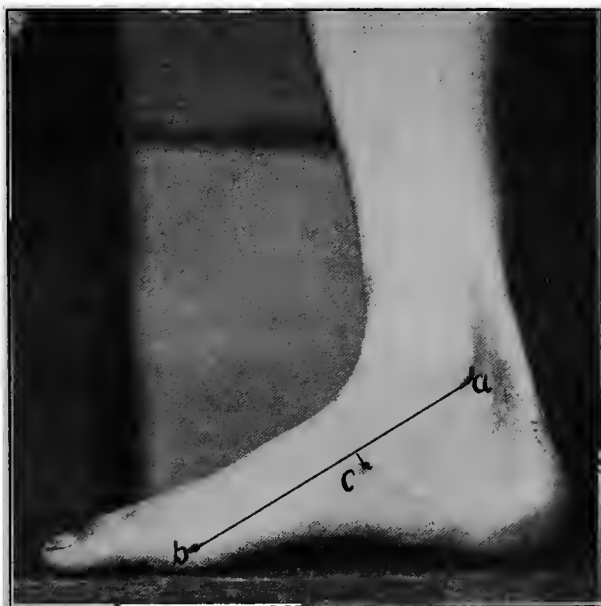


FIG. 4.—Photograph of the same foot as in Figs. 2 and 3, without weight-bearing. The posterior inferior corner of the internal malleolus, *a*, is connected with the lower tubercle on the head of the first metatarsal, *b*, by a line; *c*, represents the scaphoid tubercle.

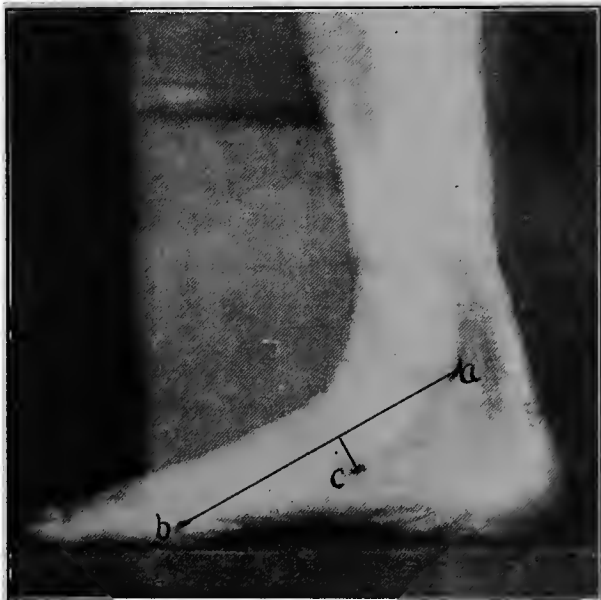


FIG. 5.—Photograph of the same foot as in Figs. 2, 3, and 4, with weight-bearing. Note the increased distance of the scaphoid tubercle from the connecting line.

a representative group of healthy young men who conduct the ordinary affairs of life.

In order to make proper observations, a standard method of estimation had to be applied. A wooden box was constructed, consisting of three sides—a base, a posterior side, and a lateral side. Its dimensions were 12 x 12 x 5 inches. The box was placed on the seat of an ordinary chair. The right foot was used. The subject stood on the floor with the left foot straight and the right knee bent. Then the right foot was placed in the box, the calf just touching the upper edge of the box, and the heel resting in the corner (Fig. 6).



FIG. 6.—Position of the foot in the box.

The weight of the body was therefore chiefly transmitted through the left leg. In this way the foot could be examined in a definite and uniform position without weight-bearing. The points marked were those landmarks earlier discussed—the posterior inferior corner of the internal malleolus, the tubercle of the scaphoid, and the lower tubercle of the first metatarsal. The distance of the scaphoid tubercle from the line connecting the internal malleolus with the lower tubercle of the head of the first metatarsal was measured as follows: A thin transparent celluloid rule provided with a scale (Fig. 7) was applied to the foot so that its upper edge coincided with the dots on the head of the first metatarsal and on the corner of the internal malleolus. Then the distance of the tubercle of the

scaphoid from the edge could be read through the transparent rule by means of the scale (the corners of this rule were cut off so that they would not interfere with the sides of the box).

SUMMARY OF IMPORTANT RESULTS. The average age of the one hundred young men was found to be 21.6 years, the youngest being seventeen and the oldest thirty-four years. The average distance

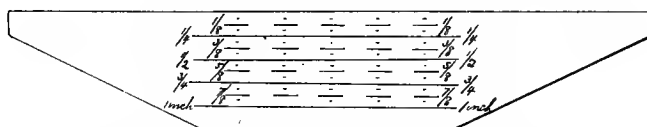


FIG. 7.—The transparent celluloid rule used for determining the distance of the scaphoid tubercle from the connecting line (reduced one-half).

of the tubercle of the scaphoid from the line connecting the internal malleolus with the lower tubercle of the head of the first metatarsal was found to be 0.49 inch.

These results, though interesting, are of less value than the results obtained by arranging the cases in a series graded according to the lowering of the scaphoid tubercle. In the following table the cases were grouped in this fashion.⁴

Distance of the scaphoid tubercle from the line connecting the internal malleolus with head of first metatarsal.	Number of cases.	Distance from scaphoid tubercle to internal malleolus.	Horizontal distance of the tubercle from vertical line dropped from internal malleolus.	Sine of angle formed by line connecting the scaphoid with internal malleolus and the vertical line.	Angle.	
					Deg.	Min.
Inch.						
0	2	2.03125	1.71875	0.8461	57	47
$\frac{1}{16}$	2	1.875	1.53125	0.8166	54	45
$\frac{1}{8}$	5	2.0875	1.7	0.1843	54	31
$\frac{3}{16}$	0					
$\frac{1}{4}$	11	2.1136	1.6843	0.7956	52	43
$\frac{5}{16}$	3	2.0625	1.6458	0.7979	52	56
$\frac{3}{8}$	15	2.1666	1.6833	0.7769	50	58
$\frac{7}{16}$	2	2.0625	1.5	0.7272	46	39
$\frac{1}{2}$	19	2.2039	1.6052	0.7283	46	45
$\frac{9}{16}$	3	2.1666	1.5625	0.7212	46	9
$\frac{5}{8}$	18	2.125	1.5277	0.7189	45	58
$\frac{11}{16}$	1	2.0	1.4375	0.7187	45	57
$\frac{3}{4}$	15	2.3	1.5	0.6521	40	42
$\frac{13}{16}$	0					
$\frac{7}{8}$	1	2.375	1.5	0.6315	39	9
$\frac{15}{16}$	0					
1	3	2.5	1.666	0.6666	41	48
Average	..	2.15	1.59	0.7390	47	40

⁴ Only the first two columns apply to the present text, but the other columns may be of interest.

The table shows that there are only nine cases in which the tubercle is less than one-fourth inch below the line, and only four cases in which it is more than three-fourths of an inch below the line. Therefore, the great majority of cases show the tubercle depressed from one-fourth of an inch to three-fourths of an inch, which in itself is a large variation (one-half inch).

CONCLUSIONS FROM THE TABLE. In studying the table we must remember that when there is a large variation within normal limits, conclusions based on only one hundred cases are of slight value; but the object of the observations was to determine the nature of the variation rather than its average extent. The important point is that the height of the arch as measured by its index, the tubercle of the scaphoid, does show this marked variation. This variation in a series of non-weight-bearing feet suggests the rule which applies to the individual foot with weight-bearing. In other words, the physiological variation (so far as the scaphoid tubercle is concerned) during weight-bearing function of the individual foot, is a prototype of the anatomical variation of a group without weight-bearing. This conclusion is one which has always been understood by the anatomists. It is simply a perhaps novel method of checking off the older observations; but the main question which is still open is, What is the normal foot? What kind of a foot are we to use on which to base the estimation of a deformity, and in what should a diagnosis of a pathological foot consist? These and allied questions require careful consideration, and to this I shall now proceed.

THE AVERAGE FOOT. It was found that in one hundred cases the average depression of the tubercle of the scaphoid from the connecting line was about one-half an inch. As earlier stated, one hundred cases are too few on which to base a fair average. But even if thousands of cases had been used it would be fallacious to reason that all feet in which the scaphoid tubercle is higher than the average, are normal, and all feet in which the tubercle is lower, are abnormal, because the average is obtained just as much from the figures below as from the figures above. Moreover, the chief point shown in the hundred cases is that there is marked variation in the height of the scaphoid in apparently healthy feet. Consequently, as the average is based on that variation, it has no significance further than what the term indicates, representing simply an average of normal variation. Such an average, therefore, cannot serve as a basis from which to estimate deformity.

THE NORMAL FOOT. The problem is not what is the average, but what is the extent of variation which we have a right to expect in the normal physiological foot? In attempting to answer this question we deal with a problem in classification, the same problem which necessarily presents itself in the study of any series of graded objects. Given a series of objects animate or inanimate, which differ from one another only to a slight extent, it is impossible to

state just where we should draw the line dividing one group from another. If we take one hundred shades of color, say yellow, and arrange these shades in a graded series from a light yellow to a brown, the differences between the individual shades which are placed next to each other are so slight as not to be detectable. Yet if we compare the beginning with the end of the series, the difference is very striking. The same holds good in a given structure in the human body in which the individuals are arranged in a series according to the variations in that particular structure. If we take one hundred feet and arrange them in a series with reference to a given point, such as the height of the scaphoid tubercle, and attempt to base a classification on that variation, it is impossible to state where the normal variation ends and where a deformity begins, although the two extremes of the series are strikingly different. This, then, is our problem; the difficulty in dividing the series is apparent; there is no natural dividing line in this arrangement which can be used to define the limits of normality. I did, to be sure, find that the great majority varied between one-fourth and three-fourths of an inch, yet I can lay no stress on these figures, because it is evident that if more than one hundred subjects had been used, the gaps between the figures would have been filled up. Nevertheless, as will be seen, such an arrangement in a graded series is of considerable importance, even if the dividing line between the normal and the pathological does not exist, because this method will help to organize our knowledge on the subject.

THE "TYPE" FOOT. It has been shown that the average foot is not a fair basis from which to estimate a deformity, and that it is not possible to make a sharp distinction in the series for purposes of classification. What, then, is a sensible method for systematizing our views? The only course which remains is to make an artificial distinction between the normal and the abnormal, but an artificial distinction which is not only practical, but which has a reasonable theoretical basis. If we study the table of the one hundred cases, we note the two extremes of the series, namely, the one extreme, in which the tubercle is not depressed at all, and the other extreme, in which the tubercle is depressed one inch. There can be no two opinions as to which extreme approximates more closely the physiological foot. There can be no doubt that the foot in which the tubercle is near the connecting line is a better foot than the foot in which the tubercle is one inch below the line. The reasons for this are twofold.

In the first place, as has been shown, the ordinary foot without weight-bearing has its tubercle higher than the same foot with weight-bearing. Now, we certainly know that the foot without weight-bearing has a greater strength and greater efficiency than the foot with weight-bearing, because the power of the former is not yet expended. On the other hand, the foot with weight-bearing is in a static position

in which part of its power is already used; consequently, a weaker foot for further purposes than the foot which has not expended its power. It seems, therefore, that, other things being equal, the higher the scaphoid tubercle is, the greater the efficiency of the foot. Consequently, if we see a large number of feet all under the same static conditions, that is, all without weight-bearing, and find this variation of elevation of the scaphoid tubercle, it must mean that those feet in the group with the highest scaphoid (of which the prototype in the individual is the non-weight-bearing foot) must approximate the highest functional extreme.

In the second place, it is apparent from what has come before, and also from a number of healthy feet in which I studied the functional power (besides those used in the present investigation), that all those feet in which the tubercles were high with respect to the connecting line presented high arches and high insteps. It is, I admit, very seldom that the tubercle falls exactly on the line, but quite a few fall very close to it, either just above or below. All feet which showed this property I have found to be extremely well formed. In addition to the elevated arch and high instep, the proportions were extremely attractive and corresponded to what an art critic would deem a beautiful foot. Why is it that the artist considers such a foot beautiful? Simply because, as part of the body, it seems well adapted to carry on its functions. From his point of view, it is a more graceful thing than when it is not so well adapted. It is, therefore, plain that the commonly acknowledged beautiful foot is not acknowledged so because some men happened by chance to call the thing beautiful, but simply because it is the natural kind of foot which seems best fitted for its purpose. In short, both from the point of view of the physiologist and from the point of view of the artist, the foot with the high arch expresses strength and adaptability to function. Therefore, such a foot connoting strength and suggesting beauty, coming naturally at the extreme of a carefully selected series, must have some significance. Why not select this as an arbitrary type, remembering, of course, the method by which the type was chosen? If we do this, and bear in mind that it is only an artificial selection, we have a fair starting point on which to base our estimation of deformity. Even if it is asserted that such a method is not completely scientific, it is at least reasonable, certainly more reasonable than having no method at all. A fairly good typical foot is illustrated in Fig. 6.

THE ESTIMATION OF THE DEFORMITY OF THE FOOT. Let me, therefore, suggest the following rule for estimating the deformity of the foot: Other things being equal, the foot is deformed in direct ratio to the deviation of the scaphoid tubercle from the line connecting the lower tubercle on the head of the first metatarsal bone with the lower posterior corner on the internal malleolus. Now, I am careful to state, "other things being equal," because I believe

that no estimation is of the slightest value without considering these other things. In any problem of this sort we have no right to take one physical sign by itself and make our estimation on that sign alone; we must always consider that point in relation to other clinical evidence. In flat foot, for example, we may have a number of considerations before us—the abduction of the foot, the pronation of the ankle, the prominence of the internal contour, etc. All these things may be correlative to the lowering of the scaphoid tubercle; if they are, we are probably dealing with a pathological foot, but if they are not, we must consider the relative value of each piece of evidence, depending in each case upon the individual circumstances of that case. I believe that the lowering of the arch is an important point in considering the deformity and that the best index for estimating the lowering of the arch is the scaphoid tubercle, but that is all the farther I am willing to go. A lowered arch does not necessarily mean a deformity, it simply means a variation; but a badly lowered arch means deformity, and what is bad we must determine in the individual case. As will be shown (Case V), a foot may be very abnormal even if the tubercle is above the connecting line. The other physical signs in such a case are more pathognomonic than the height of the tubercle.

THE CONSIDERATION OF THE SIZE OF THE FOOT. With regard to the application of the rule to individuals of different size and age, I believe that its language is sufficiently broad to cover all ordinary cases, provided that one uses reasonably good judgment in the individual. Of course, an equal lowering of the scaphoid tubercle in two feet, one large and the other small, would necessarily be of greater significance in the latter. Thus a depression of the tubercle of three-fourths of an inch in a six-year-old child is of greater consequence than an equal depression in an adult.

THE DEFINITION OF FLAT FOOT. It has been shown that the variation within normal limits in a group of feet is similar to the normal change in the individual foot with weight-bearing. From this it was naturally inferred that the more depressed a non-weight-bearing foot is, the less it is able to change with weight-bearing, and consequently that such a foot has lost part of its latent strength. Reasoning from this, I showed that a sensible classification could be made if we regarded such a foot as typical of highest function and beauty which most closely resembled the healthy non-weight-bearing foot, namely, one in which the tubercle is close to the connecting line, providing no other pathological sign co-exists. Flat foot, therefore, may be defined as a position of the bones, resembling that of physiological weight-bearing, which does not disappear when weight is removed, the amount of flattening being in the ratio of the lowering of the scaphoid tubercle.

From the above, it is clear that if we are to take such a foot as typical of beauty and function as has been described, then we can

consider few feet well formed, and that we must regard the great majority of human feet as flat. This is true; but if we regard them in this manner we must speak of the great majority as physiologically flat, or, better, as anthropologically flat. They are only flat as based on the estimation from a type, the type being based on the consideration of the highest function and beauty, and consequently, of relatively rare occurrence. It therefore becomes clear that if only a few feet are best adapted to carry on their function from this point of view, and if the great majority of feet are more or less deficient as compared with the high standard that has been set, the diagnosis of flat foot can have little practical weight unless it connotes bad function and pain. If we consider an individual foot, and note that it is moderately flat, it does not mean that the foot is unable to carry on its function; it simply means that it might have been better if it were built more according to the type. If, however, there are signs of disability accompanying the signs of depression of the arch, such as pain and muscular spasm, then our diagnosis is established. We have a similar problem in the consideration of the physical signs of other parts of the body, for example in the consideration of hypertrophy of the heart. Hypertrophy of the heart may occur in apparently healthy individuals, and may not in itself cause symptoms; but once urged that heart to carry on functions beyond the power of compensation, and it loses its resistance to future dilatation much more readily than the heart which has not previously been hypertrophied.

From what has gone before, it is evident that the use of the bony landmarks of the foot as an aid to diagnosis must be made with the greatest caution. When one considers the extreme variation in the normal, when one considers the artificial manner of selecting one kind of foot as typical, one feels some hesitation in advocating the measure as an aid to diagnosis at all. Nevertheless, if the observer is careful, he may in many cases derive some value from such a method. But if he uses it, he can never lose sight of the value of the other points in diagnosis; he simply has one more physical sign to use as evidence. If he goes farther than this and bases his whole diagnosis on that one sign, he is likely to fall into grave error.

CLINICAL APPLICATION OF THIS METHOD. If one follows such a suggestion as has been made, that of estimating the variation and deformity of a foot from the artificial type, it is necessary that the estimation should rest upon a standard method of examining the patient. Such a method has already been shown, namely, that of using a box of given dimensions, placing it at a given height, and using such a transparent ruler as earlier described. The only measure necessary is that of the distance of the tubercle to the connecting line. Simple as such apparatus is, even these things may be omitted for ordinary work. A method that I suggest is to let the patient stand on his one foot and to have him place the other foot

on an ordinary chair with the inner side of the foot facing the examiner. The weight of the body must be transmitted through the leg which is resting on the floor. Then the landmarks may be marked with a skin pencil (a good skin pencil is a grease paint pencil such as women use for painting their eyebrows), and then a simple ruler or piece of string may be applied to the points marked on the internal malleolus and the head of the first metatarsal: From this the distance of the tubercle can easily be measured. This is all the accuracy that is necessary, and requires no further apparatus. If such a box is used as has been described, it may be used both for the left and for the right foot simply by letting the patient stand on his other foot and by inverting the box. This being the method, the simple rule is: Other things being equal, the foot is deformed according to the deviation of the scaphoid tubercle from the line connecting the lower posterior corner of the internal malleolus with the lower tubercle on the head of the first metatarsal. In order to illustrate the practical applicability thereof, let me cite a few cases:

I. FEET SHOWING ASYMMETRY WITH REFERENCE TO THE ELEVATION OF THE SCAPHOID TUBERCLE. (a) *The Tubercle on the Unhealthy Side Lower than on the Healthy Side.*

CASE I.—U. B., aged twenty-two years, by occupation a barber, was first seen at my office October 16, 1908. Three months ago the patient began to have trouble in his right foot after previous good health, this consisting in disability, pain, and swelling, and had grown steadily worse. There has been no history of injury. The left foot has not bothered him and has not become swollen. Examination showed the patient limping on his right foot, which was in a position of abduction. There was swelling in the region of the internal malleolus. The skin was somewhat clammy to the touch, and the region of the swelling was bluish white. There was marked stiffness on inversion. Examination of the relation of the tubercle of the scaphoid to the line connecting the internal malleolus with the head of the first metatarsal showed it to be seven-eighths of an inch below. The tubercle of the left foot was found to be five-eighths of an inch below the connecting line. There was no swelling and no signs of spasm in the foot.

It will, therefore, be seen that the lowering of the tubercle in this case, as compared with that on the other side, is correlative to other signs, but the amount of lowering is of considerable help, showing the anatomical difference between the diseased and the other foot. The diagnosis was acute flat foot (perhaps infectious) and irritated by occupation.

CASE II.—E. B., business man, aged twenty-four years, was first seen by me September 21, 1908. Several weeks ago he strained his feet playing tennis; before this time he had had little or no trouble. Now there was pain in the right foot, especially on use, and chiefly referred to the arch and the ball of the foot. Examination showed

the feet well developed, without spasm, swelling, or calluses. There was no redness and no tenderness. In the right foot, however, the tubercle was found to be seven-eighths of an inch below the connecting line, and in the left foot five-eighths of an inch below. The inner contour of the right foot bulged somewhat more than that of the left.

It is then apparent that if the measurement was accurately made, a slight deformity was present as compared with the other foot, and it is plain that the plantar ligaments must have been weakened and stretched.



FIG. 8.—CASE III. Osteosarcoma. Note the complete obliteration of the arch out of proportion to the amount of lowering of the scaphoid tubercle.

CASE III.—F. F., aged thirty-nine years, a laborer, was first seen at the Lakeside Dispensary August 10, 1908. One year ago the right foot began to swell and the patient noticed his arch lowering. The swelling became worse and the arch grew flat. He had some pain and limped. He was treated for flat foot. Examination of the foot (Fig. 8) showed marked swelling, including the whole tarsus from the ankle to the metatarsal region. The foot seemed completely flat. The bony landmarks could not be distinctly felt. What seemed to be the tubercle of the scaphoid was one-half an inch below the connecting line; that on the other foot was about one-fourth of an inch below the connecting line.

Here we had an apparent incongruity of facts. There was bulging

of contour, marked flattening of the arch, and marked swelling, whereas the tubercle, which, if it were a flat foot, should have been markedly depressed, was only one-half an inch below the line. A Röntgen picture was taken and showed plainly that a mass of bone and new tissue had formed and included the whole tarsal region. The diagnosis of osteosarcoma was made. The seemingly contradictory evidence was the reason for taking the Röntgen picture, because, if the arch were as flat as it seemed to be from inspection, the tubercle should have been much lower.

(b) *The Tubercle on the Unhealthy Side Higher than on the Healthy Side.*

CASE IV.—M. G., a servant, aged about thirty-five years, was first seen at the Lakeside Dispensary October 19, 1908. The preceding April she sustained a fall of eight feet, landing on the sole of the right foot. The foot became swollen, and has disabled her since. She had been treated at another hospital by having the foot strapped. There had been some relief. The pain was chiefly on the outer side of the foot. Examination showed the right foot permitting almost no motion in inversion, but fairly good motion in dorsal and plantar flexion. The restriction of motion seemed to be chiefly due to mechanical bony interference rather than spasm. Some induration was to be felt under the malleoli and on the dorsum near the cuboid. The tubercle of the scaphoid on the affected side, the right, was one-eighth of an inch below the connecting line, and on the good side three-eighths of an inch below. A Röntgen picture was taken and showed a lesion of the calcaneo-astragalar joint, and signs of impaction in the astragalus with fusion of the calcaneo-cuboid joint.

It seemed that in the original injury the astragalus had been crushed into the os calcis, indirectly injuring the cuboid. This anatomical lesion would explain very well the relative elevation of the tubercle of the scaphoid on the affected side, because the malleoli had been lowered by the crushing of the joint beneath, whereas the position of the scaphoid had not become altered.

CASE V.—M. K., a school boy, aged about twelve years, had infantile paralysis when a child, causing the present deformities. Examination showed the left foot in the position seen in Fig. 9, with the dorsum very high, the toes markedly contracted, the dorsal flexors of the toes prominent, the arch extremely high, the ball of the big toe prominent, and the plantar fascia very tense. This kind of a foot is immediately recognized as a claw foot or non-deforming club foot. The other foot was in equinus, so that it could not be used as a healthy foot for comparison. Measurement of the scaphoid tubercle on the claw foot showed it to be one-fourth of an inch above the connecting line, indicating the extreme elevation of the arch.

The first three cases hardly require additional comment, except to

call attention to the fact that the measurement of the relative depression of the scaphoid tubercle is of considerable help when making comparison with the other foot. In Case IV the reasoning from these landmarks should have carried with it a diagnosis of fracture, even without a Röntgen picture. In Case V the tubercle is actually elevated above the connecting line. It might be thought that, according to our rule, in which it is stated that the foot is deformed according to the deviation of the scaphoid tubercle from the connecting line, there would be confusion in distinguishing such a foot from the "type" foot, but this case brings out the point on which I laid special stress, namely, that other things have to be equal. Here, to be sure, the scaphoid tubercle is markedly elevated, and



FIG. 9.—CASE V. Claw foot (non-weight-bearing) from infantile paralysis. Note the elevation of the scaphoid tubercle.

would by itself suggest beauty and function, but the cause of the high elevation, the paralysis (namely, paralysis of the interossei), has also brought about coincidental deformities, that is, contractures. In other words, other things are not equal. There are pathological signs which make up for the height of the arch, and the co-existence of these other pathological signs and symptoms would prevent us from calling such a foot a "type" foot.

II. SYMMETRICAL DEPRESSION OF THE SCAPHOID TUBERCLE
These are the most common group of cases, and, of course, include the ordinary flat foot.



FIG. 10.—CASE VI. Flaccid flat foot of moderate degree (non-weight-bearing) in a subject aged ten years. The tubercle is $\frac{3}{4}$ inch below the connecting line.



FIG. 11.—CASE VII. Rigid flat foot, marked (non-weight-bearing). The tubercle is one inch below the connecting line.

CASE VI.—F. M., aged eleven years, was seen at the Lakeside Dispensary, March 15, 1908, complaining of pain in both feet for some time. No swelling was noticed. Examination (Fig. 10)



FIG. 12.—Röntgen picture of Case VII. The metal mark shows the position of the scaphoid tubercle.



FIG. 13.—Severe valgus following infantile paralysis. The mid-joint represents not the tubercle of the scaphoid, but the head of the astragalus.

showed the feet long, lanky, and abducted. There was no stiffness, and the arch was apparently low. The tubercle of the scaphoid was about three-fourths of an inch below the connecting line on each foot without weight-bearing. A diagnosis of moderately flaccid flat foot was made.

CASE VII.—W. H. Five years ago this boy began to limp. His ankles and wrists became swollen. Since then he has stumped about with his feet in the same condition, and has had much pain and swelling. Examination (Fig. 11) showed marked valgus, abduction, and pronation of the ankles, which were swollen and bluish. On palpation the tubercles of the scaphoid were found to be very low, about an inch below the connecting line. The peroneal tendons were tight. There was stiffness in all directions. The patient toed out when he walked. In this case I placed a metal mark on the tubercle and took a Röntgen picture, which proved that this prominent point on the contour was really the tubercle (Fig. 12). A diagnosis of extreme rigid flat foot was made.

Both these cases illustrate common types of flat foot and the relative significance of the depression of the scaphoid tubercle as suggesting the severity of the deformity.

It is, perhaps, worth while to call attention to a possible source of error. In very severe types of flat foot (as from infantile paralysis) the head of the astragalus twists so far inward as to suggest that its prominence is the tubercle of the scaphoid (Fig. 13). Experience and the study of the skeleton, however, will prevent the observer from being misled.

The Estimation of the Amount of Paralysis in Infantile Paralysis from the Point of View of Operative Treatment (Tendon and Muscle Transplantation, Etc.)

By HENRY O. FEISS, M. D., Cleveland.

The object of a tendon transplantation in infantile paralysis is to render a joint, made partially useless by the paralysis, more useful by increasing its stability, or increasing its function in a certain direction. This is done by distributing tendinous insertions of muscles about the joint, so that they have the greatest possible mechanical advantage, and is accomplished by substituting good tendons, either in part or in toto, from parts where they can be easily spared, and inserting them into other parts where they are of relatively great advantage. To attain this object, we must know definitely which muscles are functioning and which are paralyzed.

It is commonly supposed that the best evidence as to the paralysis of individual muscles from this disease is by means of electrical reactions, that is by testing for the reaction of degeneration. Scientifically speaking, there is no question as to the great importance of this method, but the value of this test, in deciding upon the kind of operation necessary, is usually overrated. In the first place, the method is difficult of application, especially in young children; in the second place, it takes considerable time, and in the third place, the deductions to be drawn are seldom more than those that could be drawn from the simpler methods. For these reasons, almost all men of experience, so far as I know, have come to the conclusion that as a means of diagnosis of the paralysis of individual muscles, electrical reactions have very little practical significance; hence, they seldom use them.

The most important method in testing the activity of an individual muscle or group of muscles is to elicit certain definite movement in the limb tested. If, for example, we wish to test the quadriceps, we ask the patient to extend the leg, and if the patient does so without rotation, it connotes function of that muscle. The value of this method is its simplicity. It may be stated as an argument against this method that the child may be too young to know how to respond actively. In that case an excellent and simple method is to tickle the skin of the limb, thus eliciting a reaction of whatever active motility may be present. Such light stimulation of various parts of the skin will make the limb respond definitely in certain directions according to the area stimulated.

Here it may be said, however, that if the child is too young to know how to respond actively, it is usually too young to be operated upon. This is so, because in infantile paralysis an operation must never be thought of until the natural recovery has reached its full extent. So if a child of two years or younger, has infantile paralysis, it is rarely of practical value, it seems to me, to know accurately just which muscles are paralyzed, because we cannot at any rate consider an operation at that time. Months and often years must elapse before we have a right to be certain that the paralysis has reached a permanent phase, and that no further recovery is taking place. By that time almost all children will possess sufficient intelligence to know how to respond by active impulse.

A third method of testing the muscles is by having the child attempt certain motions against resistance. This is the best method of all when the child is intelligent enough to understand. For example, to test the gastrocnemius, the palm of the examiner is placed against the ball of the foot and the child is told to bend the ankle downward (plantar flexion). If there is any power it will be felt by the examiner and the tendo Achillis itself will stand out so as to be visible as well as palpable. For the tibialis anticus and posticus, resistance is placed on the inner side of the foot; for the peroneals, on the outer side; and for the dorsal flexors, on the dorsum, etc. This method tells us not only whether

the muscles are functioning but gives us a rough estimation of the amount of power in the muscles tested.

To summarize then, the electrical reactions have their place in diagnosis when it is desirable to attain great scientific accuracy and when the subject is favorable, but in ordinary practise the best methods of testing the function are voluntary impulses on the part of the patient, reflex impulses from stimulating the skin, and thirdly, active impulses against resistance.

Finally, it may be added that if we have decided upon a tendon transplantation the final test of the muscle, whose tendon we are to transplant, is its actual appearance at the time of operation. For example, not long ago it was my intention to transplant the sartorius into the quadriceps, the latter having been paralyzed. I made the incision on the inner side of the patella and exposed the sartorius but noticed at once that it was blanched and atrophied, whereas the color of a healthy muscle should be deep red. For this reason I decided not to touch the sartorius but through the same incision went down to the semi-membranosus, which was found to be good and strong and worthy to be transplanted. This I did. So in any other operation, even if the incision is made, the operator can always change his plan if he finds the muscle he hoped to use is not sufficiently strong.

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The Essentials in the Treatment of Non-Ambulatory Cripples Deformed by Infantile Paralysis

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The term "non-ambulatory" is used for lack of a better one. It refers to those patients who have become so deformed by infantile paralysis that they are unable to stand or walk, and the chief object of this paper is to show how they may be placed on their feet. The cases are not uncommon, especially among the poorer classes. The chief cause of the condition is the fact that after the original paralysis, recovery has been permitted without any regard to the contraction of the good muscles. The result is that the joints contract, so that even if there is sufficient power left in the muscles about the joints to permit stability, the contractures prevent them from being placed in positions where this power can be properly applied. In cases where there have been no contractures, the non-ambulatory condition is due to failure to use proper mechanical measures. Of course some of these cases are hopeless.

Occasionally, we find that the only contractures are in the feet and ankles. If such deformities (equinus, equino-varus, etc.) are marked, they might alone in early childhood prevent standing and walking, and in such cases the treatment simply consists in correcting these deformities.

More frequently, the cause of the disability is the contracture of the hamstrings of the knees and the anterior flexors of the hips. The treatment of such cases requires the most careful attention and perseverance; the difficulties increasing in direct ratio to the age of the child and also in relation to the length of time from the original onset. If a case is seen early, that is soon after the deformity has taken place, gradual straightening can often be brought about by means of simple braces, splints or plasters. It is usually found that the contractures of the hips are secondary to the flexures of the knee. For this reason, if the knee contractures are straightened out the hips will often straighten themselves, owing to the weight of the extended limb. The straightening out of the knee contractures is not always a simple procedure.

Read before the Academy of Medicine of Cleveland, October 15, 1909.

It is commonly believed that if sufficient force is applied the knee will straighten out and once made straight, the case is disposed of. This would be true if it were not for the danger accompanying the procedure. One has no right to use too much force in the correction of the knee, because if such a knee has been in a position of permanent flexion for years and is then straightened out all at once, the vessels and nerves will be placed on a sudden stretch and changes in the circulation might arise and, in some cases perhaps, even lead to gangrene. Therefore, this correction must be made with the greatest care.

If the case is of long standing, the best way is to etherize the patient and to use a moderate amount of force. If headway is made, further manipulation with or without ether, by changes of plasters or by caliper splints may finish the correction, but when this is not sufficient, an open operation is to be done and the hamstring tendons are to be lengthened by some simple method. After the correction of the knee by either of these methods, the foot must be watched for change of color. If there is any noticeable changes in the circulation the plaster must be removed and a little flexion allowed for the time being. In a few weeks or months another manipulation will probably finish the straightening. The same precautions are, of course, necessary at the ankle if the foot is badly deformed.

With regard to the hip, it is difficult to gain much by the application of force. In the attempt to extend the thigh, lordosis takes place in the lumbar spine so that little is really gained in the hip joint itself. Here it is advisable to do an open operation over the contracted part, which is almost always the tensor vaginae femoris, and simply divide the tight strands. In this operation, it is surprising how many contracted strands will be found. After these are divided, no great correction is usually gained and the surgeon is liable to become badly discouraged, but after a few days, he will notice the leg coming down farther, and if he lays the patient on a padded board or Bradford frame and binds down the pelvis and knees, he will soon have the hip straight. In some cases passive motion exerted every day after the first week or so will hasten the correction.

It is apparent from the anatomy of the parts that little leverage can be gained at the hip unless the knee is straightened out first; then, with the leg straight, the correction at the hip can proceed without much difficulty. Moreover, as stated above, the weight of the whole leg acts as a force in maintaining the straight-

ness of the hip; whereas, if the knees were bent such weight could not be applied.. Often after the attempt to straighten out the hip, there is some lordosis left on account of residual hip contraction; usually, however, if the patient is not too old, even this gradually obliterates after the patient stands, because the tendency of the human frame in standing and walking is to stretch the anterior thigh muscles.

The above procedures form the first essential part of the treatment of these non-ambulatory cases—namely, to straighten out every deformity in the ankle, knee and hip by gradual correction when it can be applied, or if necessary, by forcible manipulation under ether or finally, by cutting operations when force alone is not sufficient.

Assuming now that the patient has been properly straightened out, the next stage in the treatment must be to attempt to get the patient on his feet. It is wise in many cases, to put on the simplest form of apparatus and I have been accustomed to use so-called "caliper" braces (these are temporary braces to be replaced later by permanent ones), which consist of two uprights of round stock running into the heel of the shoe below and ending above in a perineal ring. A strap is placed behind the knee to prevent hyperextension and a knee-pad is placed in front of the knee to prevent flexion. Such a brace insures stability in the whole leg up to the hip. If there is any tendency to recurrence of equinus, simple stops can be placed at the heel to prevent this deformity, or straps may be run from the sole of the shoe to the uprights, which can be adjusted so as to hold the ankle at the desired angle. After these are properly adjusted and the patient has become used to wearing them, he is given crutches and in most cases learns to walk with them very soon. After a few months the patient is told to try to discard the crutches and to take steps for himself. This having been achieved, then is the time for reconsideration of the case with regard to plastic operations on the muscles and joints with the hope of eventually discarding one or both braces, or changing from a knee-brace to an ankle-brace. The choice of operation here depends entirely on the conditions in the individual case. We must consider tendon transplantations, shortening or lengthening of tendons, arthrodeses, excisions, etc., every joint being considered by itself.

As the main object of this paper is to show how these patients may be put upon their feet, the further treatment (permanent braces and operations) will not be considered here, but in the

report of the cases which follows, brief mention is made of some of the subsequent steps.

The only contra-indication for the above treatment is when the mechanical conditions for recovery are so bad that the case is hopeless. For example, if the spinal muscles and hip muscles are all paralyzed, and when the child has no power in the shoulders, elbows and hands to hold crutches. Practically all other cases may be placed upon their feet.

Following is a summary of nine cases, which have been selected to show the various steps which have been taken. All of these were helpless when first seen and crept about the floor. All of these have now been enabled to walk, some with crutches, some with braces alone, and some with but one brace.

Case I. E. J., aged 22 months, was first seen at Lakeside Dispensary, March 29, 1909. A year ago was taken with paralysis and made progress until a month ago.

Examination showed the child not able to stand or walk. Seemed to have power in the quadriceps and hamstrings on the left side but none in the foot on that side. Could extend the right knee in external rotation; this foot under control. May 13, 1909, caliper splints were applied. The child is now beginning to stand and walk. Here no operation has yet been advisable.

*Case II. S. J., aged four, was first seen in the Lakeside Dispensary March 21, 1908, the paralysis having begun two years previously.

The examination showed pretty good control of the left leg except that the foot was in valgus. The right knee was not under control either in flexion or extension and the foot was in marked varus. Child could neither stand nor walk.

June 1, 1908. The right tendo achillis was divided and a brace was applied to the right leg holding the knee straight and the foot at a right angle. Later on, the tendo achillis on the right foot again contracted and a tenotomy was done at Rainbow Cottage. Examination July 9, 1909, showed the child walking with a brace and without her crutches.

Case III. N. M., aged four, was first seen at Lakeside Dispensary March 10, 1908. Taken with paralysis while an infant. The case was originally treated by Dr Dudley Allen, who kindly assigned it to the author for further treatment. When first seen by him the child could not stand or walk, although there was little contraction. He ordered braces and with the help of these and crutches, the child learned to stand and walk. On June 13, 1908, the child was walking without crutches with the help of both braces. March 24, 1909, operation: the tendo achillis divided on each foot and the iliotibial band transplanted into the quadriceps on the right. The child is now walking fairly well but is still using a brace on the right leg.

Case IV. A. S., aged eight, was first seen at Lakeside Dispensary Sept. 19, 1909. Paralysis had begun three years before. There had been no improvement since. Examination showed both legs very thin and no control of either ankles or knees. The right hip in a position of 45° flexion. Child could neither stand nor walk. Sept. 23, 1908, operation: the tensor vaginae femoris was divided. The tendo achillis divided on the right foot. When last seen, July 1, 1909, child was walking with caliper splints and crutches.

*For the treatment of cases II, III, IV and V in the hospital wards, I am indebted to the kindness of Dr Dudley P. Allen.

Case IV. A. B., aged three, was first seen at Lakeside Dispensary May 19, 1908. This child was taken with paralysis at the age of nine months. Examination showed thighs abducted, knees flexed and ankles extended. Child could neither stand nor walk. Each leg showed that it could adduct and move the thigh pretty well. Flexion of the knee permitted, but no power in extension. The hamstrings were short. Some power in eversion in the ankles. Each tendo achillis was contracted. June 1, 1908, operation under ether: knees forcibly corrected. Tendo achillis lengthened on each foot by open operation. June 28, 1908, patient has learned to walk by means of caliper braces and has discarded crutches. Condition then showed recontraction of the tendo achillis but the knees straight. June 29, 1909, operation under ether: on the right the sartorius transplanted into the quadriceps tendon and the biceps transplanted into the tubercle of the tibia by means of silk lengthenings. Each tendo achillis tenotomized. Later the silk sloughed out, but the sartorius has held. Similar operation to be done later on the other knee. Child still using caliper braces, but will undoubtedly discard at least one later on.

Case VI. E. P., three years old, was first seen Sept. 21, 1906. The paralysis began at the age of two years and the child could only creep and sit. Examination showed a small, anemic child with right hip in right angle abduction. No control of the knee or ankle. Oct. 5, 1906, under ether, tenotomy of the tight bands running from the anterior superior spine. Hip straightened and put up in plaster. Child learned to walk in this plaster and improved. A brace was applied February 1907, and since then the child has learned to walk alone.

Aug. 7, 1909. Child is walking without crutches but with a permanent brace on the right leg. This brace holds the knee straight and prevents toe-drop. Child almost ready for an operation on the knee, transplanting the sartorius and later, to have an arthrodesis of the ankle.

Case VII. F. Q., six years old, was first seen July 7, 1908. Taken with paralysis at the age of one year. Examination showed both knees and hips drawn up. Hips could not be passively extended. Tensor fascia very tight. The contraction less than a right angle on the right. Very little less contraction on the left. Both knees drawn up tight and could only be extended to 45° of straight. No quadriceps. Hamstrings present on the left and partly deficient on the right. The hips besides being flexed were also abducted, so that the child lay in a frog position. Child could neither stand nor walk. July 23, 1908, operation under ether: attachments of the tensor vaginae femoris and a mass of other muscular tissue and bands were divided at both hips. This permitted the thighs to come down to an angle of 120° . The knees were forcibly corrected to about 40° of straight. Then the pelvis, thighs and knees were encased in plaster and the child was placed on a Bradford frame. Caliper splints were applied on July 28, because the plaster was very uncomfortable.

Aug. 29, 1908. Patient was learning to walk with crutches, both hips having been brought down by passive motion to 35° of straight. The knees were almost straight. Oct. 21, 1908, there was no deformity left, even with the braces off. On May 20, 1909, the status was as follows: She can extend neither knee. Has no control of the right ankle but it is not in a position of permanent deformity. She dorsal and plantar flexes the left foot. She walks alone with the caliper splints. July 13, 1909, plastic operations were attempted at the knee. These have been succeeded; nevertheless, she will be enabled to walk with the help of light knee braces.

Case VIII. M. McK., aged seven, was first seen November 14, 1905. She was taken with severe paralysis at the age of three and a half, affecting both legs and the left arm. The arm recovered. Examination showed both hips in slight position of abduction and flexion. Knees were contracted to a right angle. Tendo achillis in both ankles tightened. Very little control over either foot. Child unable to stand or walk.

An operation was done May 2, 1907. On the right knee the hamstrings were divided. Same on the left. Each tendo achillis also lengthened. Gradually the legs became straighter and she got caliper splints May 18, 1907. She was walking June 25, 1907, with the help of crutches and braces. In the summer of 1908, a tendon transplantation was done on the right knee using the outer hamstrings and one of the inner ones. The result of this is not yet certain, but she is walking now without crutches and with the use of her braces alone. The reason that the knee operation is not certain is because the foot is still in a very bad position of varus which will have to be corrected before she can stand without a brace.

Case IX. M. S., aged 11, was seen first Jan. 27, 1908. Taken with paralysis the previous September. The attending physician allowed her knees to contract. Examination showed the left leg in a position of 25° permanent flexion at the knee on account of the tight hamstrings. The right was more flexed than the left. She had apparently complete control of the left side except for the contraction. The right was atrophied and showed apparently a paralysis of the quadriceps and tibialis posticus, the peroneus longus being very active.

No operation was necessary here, the case being seen recently enough after the onset. Caliper braces were applied with the intention of gradually straightening out the legs. This was easily accomplished with the help of a good nurse. Passive motion was also used. On March 8, 1908, she had complete control of the left which was straight: patient very much improved and could stand alone with the brace only on the right leg and walk with crutches. March 18, 1908, patient was walking without crutches and with the brace only on the right leg. April 10, 1909, a very simple leather brace with two uprights was applied to hold the right knee steady, and the girl is still wearing this without the help of any other apparatus and getting about. Later a transplantation may be done on the right knee so as to do away, if possible, with all apparatus.

418 Lennox Bldg.

The Breus Mole.

By A. H. BILL, M. D., Cleveland.

The peculiar malformation of the ovum which is generally known as the Breus mole or hematommmole is of interest not so much on account of its pathologic significance as on account of its most interesting and unusual form and development.

The clinical history of the case, the appearance of the ovum both macroscopically and microscopically, its development and formation, and the atypical development of the embryo are so characteristic and differ so entirely from those of any other normal or pathologic ovum, that it is generally recognized as a distinct variety of the moles of pregnancy.

The mole was first described in 1892 by Breus in a monograph entitled "The Tuberos Subchorial Haematoma of the Decidua." Breus reported five cases, and laid down the following as their essential characteristics:

1. That there is a marked disproportion between the size of the embryo and that of the ovum, and also a marked discrepancy between the apparent ages of both ovum and embryo, as determined by their size and development, and the period of pregnancy, as obtained from the history of the case. In the most striking of Breus' cases the patient had given a history of pregnancy of 11 months' duration, while the ovum expelled had

Read before the Clinical and Pathological Section of the Academy of Medicine of Cleveland, June 4, 1909.

merely the size of a three months' pregnancy and the embryo had a length of merely 1.5 cm.

2. There is an absence of any circulation between the fetus and the placenta; that is there is an absence of blood-vessels in the chorion.

3. The presence on the inner or fetal surface of the placenta of hematomata which, covered with amnion and chorion, bulge into the cavity of the ovum.

There have been altogether about 35 cases of this mole reported by various writers.

I wish to report and show the specimens of three typical moles of this variety.

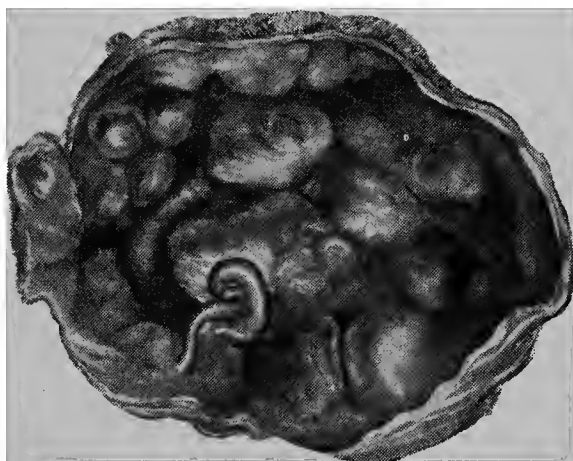
1. The first case is reported through the courtesy of Dr W. T. Howard. It is that of a woman 37 years of age who had previously had nine children. Her previous labors were normal and her past history was negative as to general or pelvic disease. The last menstruation was in August, 1905, the exact date not being remembered. In September and October there was nausea and vomiting and suppression of the menses. In November there was a slight menstrual flow for one day, which was the last until March 17, 1906, when a moderate hemorrhage occurred and recurred irregularly for one week until March 24, when the ovum was expelled intact. The general health of the patient had been good up to this time and her convalescence was perfectly normal.

The ovum which was expelled measured $5\frac{1}{2} \times 8$ cm., and contained about two ounces of amniotic fluid. The ovum and embryo were in a good state of preservation. The placenta, which was well formed, covered about one-half of the ovum, while over the chorion laeve there were still remnants of decidua. The external appearance of the ovum showed nothing unusual. On the inner surface of the placenta are to be seen numerous spherical and irregularly shaped protuberances varying in size from 2-3 mm. in diameter to 2 cm. in diameter. These protuberances project into the cavity of the ovum several mm. to 1 cm., and are covered with the smooth and glistening amniochorion. They are of a dull reddish-blue color. Toward one edge of the placenta is to be seen the embryo, attached by a small umbilical cord 8 mm. in length, the latter apparently being inserted directly into one of the protuberances. On section these protuberances appear as homogeneous, red, partly organized masses of blood, hence the name hematommole.

The embryo is 9 mm. in length, shows marked curving of the body and shows very distinctly the buds of the upper and lower extremities. There is no trace of the umbilical vesicle to be seen. The embryo corresponds in its development to about $3\frac{1}{2}$ to 4 weeks. The ovum in size corresponds to a growth of three months.

Thus we have a history of seven months' pregnancy, an ovum the size of three months and an embryo the size and development of $3\frac{1}{2}$ to 4 weeks.

2. The second case is that of a woman 26 years of age who had already borne two children. The past history, as in the previous case, was negative. The first two pregnancies and labors were perfectly normal and the general condition of the patient was fair, although she was not a very well nourished woman. The last menstrual period was during the last week in February, 1908. After the cessation of the menses there were the usual symptoms of pregnancy, including nausea and vomiting, although the latter was not at all severe. On June 28 the patient menstruated for three days, apparently about as usual and concluded she was not pregnant. After this there was no hemorrhage until August 25, when a flow began, associated with pains. With rest in bed this subsided, but recurred on August 28, when the ovum was expelled intact. As there



Breus Mole, Case No. 1.

seemed to be some of the placenta missing from the ovum and as the hemorrhage did not cease as well as desired, the uterus was curetted and some small pieces of retained placenta removed. Convalescence was perfectly normal. The patient had previously shown no toxic symptoms from retention of the ovum.

The intact ovum in this case measured $4\frac{1}{2} \times 5 \times 8$ cm. and contained about two ounces of clear straw-colored fluid. On the inner surface of the placenta, which is very well formed, are to be seen the characteristic hematomata, which in this case are considerably smaller than in the previous case. In this case there is also no trace of the yolk sac. The embryo measures 11 mm. in length and is attached by a cord but 7 mm. in length. The embryo shows practically no curving, but the buds of both the upper and lower extremities are to be made out distinctly. The eye is also to be made out.

The age of this embryo is evidently about four weeks. The ovum corresponds in size to about three months. The history of pregnancy is that of six months' duration.

3. The third case is that of a primipara 19 years old. The general health of the patient was good and the previous history negative. Menstruation was always somewhat irregular, usually varying from every three to every four weeks. No history of any uterine or pelvic disease could be obtained. The last menstrual period was Nov. 24, 1908. Beginning the latter part of December and during the first half of January there was morning sickness. During the first week in February there was a menstrual flow for two days. On April 25, 1909, there was again flowing, continuing until April 28, when pains started and the patient expelled the ovum and embryo. The ovum had previously ruptured and the fluid had escaped. The uterus was curetted and some shreds of placenta removed. The patient got up from bed and went to work in a restaurant the next day regardless of orders, but made an uneventful recovery in spite of it.

The placenta in this case measured about 5.5×7 cm., so that the whole ovum was apparently about the same size as the two previous ova. The inner surface of the placenta is somewhat more irregular than in the other cases and the protuberances are larger. The embryo is only 5 mm. in length and is apparently somewhat malformed. Very little can be made out in regard to its development macroscopically, but it probably did not live more than three weeks, as determined by its size. As in the other two cases there is no trace of umbilical vesicle.

Microscopical examination of sections of the mole, including the hematomata, shows the following:

The amnion and the superficial chorion, that is that over the surface of the placenta, and also the chorion laeve are practically normal. The protuberances themselves are made up almost entirely of blood in a more or less advanced stage of organization, while there is occasionally seen a trace of a dead chorionic villus in this mass.

The primary villi of the chorion show comparatively little tendency to branching and there is a noticeable scarcity of secondary villi in these areas, those present being in a more or less marked stage of degeneration.

Upon examination of the secondary villi a striking feature is the condition of the epithelium which, over the best-preserved villi, consists of but one complete row instead of the two rows of Langhans' cells and syncytium which should be present at this stage of development, and this in places is very low and in others entirely absent. It is noteworthy that over the part of the villi devoid of epithelium there is a deposit of fibrin, and the villi, entirely devoid of epithelium, are seen embedded in fibrin, while around those with intact epithelium there is free uncoagulated blood. Some beautiful examples are seen of villi only partially devoid of epithelium on which there is a heavy deposit of fibrin over the denuded area alone, while the remaining part floats free in the blood. These areas show the similarity between the epithelium of the villi and the endothelium of the blood-vessels in their function of allowing blood to flow over their surfaces without coagulation, a fact very important in the early formation of the placenta.

In the chorionic villi no traces of blood-vessels are to be found, thus a fetal circulation has, of course, not been established.

Another noticeable feature is the persistence of the trophoblasts, which appear occasionally in isolated groups, but for the most part near the decidual surface and in intimate relation with the decidual vessels, which they are apparently opening up. As they evidently do this in part at least, independently of the villi there results a diffuse flow of blood into the intervillous space.

The decidua compacta shows few abnormal changes; the chief change being a slight degree of round-cell infiltration.

The fact that the age of the embryo in these cases corresponds so nearly with the usual time of vascularization would lead to the idea that the sudden cessation was due to the death of the embryo, and it is noteworthy that in all cases of the Breus mole reported the embryos have died before vascularization of the chorionic villi has been accomplished. It is also of note that in none of the cases has the umbilical vesicle been observed, and since this must be the chief source of nutrition of the embryo, its absence may have a bearing on the death of the embryo.

Various theories have been advanced in explanation of the formation of these hematomata. Thus Breus explained their formation by an outpouring of blood from the decidual vessels into preformed sac-like folds of the amniochorion, and thought that this folding was brought about by a disproportionate growth of the membranes after the death of the embryo, at the same time claiming that in the death of the embryo lay the ultimate cause of all.

Davidson attempted to explain their formation by the presence of an hydramnios at an earlier stage in the course of the pregnancy, the fluid having been absorbed later on, thus leaving a considerable diminution of pressure within the sac and a consequent tendency to an inward bulging.

Bauereisen declared the direct cause of the formation of the hematomata to be the stoppage of the outflowing blood by detached chorionic villi which occluded the veins of the decidua. He suggested the name "aneurysmamole," since according to his theory there were really dilatations of blood-spaces rather than extravasations.

Walther suggested an endometritis as the cause of the mole, but in practically none of the cases was an endometritis reported.

The hematomata are apparently formed between the large primary villi in spaces formed by the necrosis and breaking off of the secondary villi. The persistence of the trophoblasts and the progressive opening up of new decidual vessels, often appar-

ently independently of the villi, would lead to the continual addition of new blood-streams. Under the pressure of this blood, increased by the uterine contractions which are going on at this early stage of pregnancy, distention can take place in only one direction, that of the amniochorion which offers the least resistance.

The increase in the size of the hematomata is thus due to a mechanical stretching of the amniochorion and may go on to a considerable extent, sometimes giving them a pediculated or stem-like appearance, a fact of which Breus made special mention.

There is no evidence that syphilis may be a causative factor as in practically none of the cases can a syphilitic history be obtained. Dr O. T. Schultz examined sections of the first specimen for evidences of syphilis and could find none present.

As to the further changes which the ovum and embryo may undergo after long retention in the uterus very little is known. The embryos are usually very well preserved even after 11 months' retention, as shown in one of Breus' cases. Mickolitch reported one case of Breus mole, with the formation of bladder-like sacs in the chorionic villi, giving a picture very much like the hydatidiform mole, the only case of its kind on record; but while there may be a marked edema leading even to the formation of these bladder-like sacs, none of the other characteristics of the hydatidiform mole are shown, there being no tendency toward an excessive growth of the epithelium of the villi but rather a retrogression.

There is no record of any case leading to metastasis or showing any signs of malignancy as in the hydatidiform mole. This fact naturally has a distinct bearing upon the treatment that should be followed in these cases.

Symptoms: The clinical picture is that of a "missed abortion." The age of occurrence is less than that of the hydatidiform mole and is usually between 25 and 35 years, that is at the time when abortion is most common. It occurs more commonly in multiparous patients than in primiparae, one case reported being that of a woman in her twelfth pregnancy. The previous history may be entirely negative and usually there is no history of endometritis or of previous abortions, although in one case the patient had aborted four times during the previous year. In Walther's case the patient had previously had two hydatidi-

form moles, but otherwise there had been no abortions. Taussig saw two Breus moles in the same patient. At first there are the ordinary symptoms of pregnancy, the cessation of menses together with all the subjective and objective signs. But after a long period of amenorrhea there is not a proportional increase in the size of the abdomen, the uterus usually not growing beyond the size of three or four months' pregnancy.

The longest period of retention of the ovum reported was 11 months. In about three-quarters of the cases there was bleeding, often several months before the expulsion of the sac, and occasionally so marked as to be an alarming symptom. The hemorrhage is usually accompanied by pain in the abdomen. The expulsion is usually not accompanied or followed by fever.

Diagnosis: This is usually not made before the expulsion of the ovum as it is difficult to distinguish it clinically from the ordinary retained ovum. In the latter, however, there is often a foul-smelling discharge accompanied by fever and general disturbances, symptoms which have not as yet been observed in cases of Breus mole. The physical signs are directly opposite of those seen in the case of the hydatidiform mole, in which the uterus grows out of all proportion to the duration of pregnancy. A summary of the clinical and pathological characteristics which will serve in the diagnosis is as follows:

1. The marked disproportion between the size of the embryo and the period of gestation.
2. The relative absence of symptoms of intoxication from the long retention.
3. The disproportion between the size of the embryo and that of the ovum.
4. The presence of the tuberos hematomata, which may be lobulated and have constricted bases.
5. Lack of blood-vessels in the chorionic villi.
6. The poor development of the epithelium of the chorionic villi, which may be entirely absent, the layer of Langhans' cells being particularly poorly formed.
7. The persistence of the trophoblasts.
8. The poor development of the embryo, which usually corresponds in size to that of four to six weeks.

Prognosis: This is good: there is, as a rule, no recurrence, although one case has been reported in which a second hematoma was formed within a year. There is no infiltration of the

uterine wall by the mole. The only troublesome symptom, the hemorrhage, while in some cases rather severe, has never proved to be a serious complication. The presence of broken off villi in the decidual vessels, which was described by one writer, suggests the possibility of embolism, but this has never yet been observed.

310 Osborn Bldg.

Typhoid Fever Complicating Pregnancy.

By WM. O. ZIEMER, M. D., Cleveland

The history of the study of typhoid during pregnancy may be said to begin with the observations of Louis in 1829. As to the frequency of this complication, statistics are not very accurate. Liebermeister in 1,420 cases found but 18 associated with pregnancy and Zuelzer in a series of 1,852 cases at Vienna, found but 24. Thus the percent runs between 1.2 and 1.3, but these statistics make no distinction as to age or sex. At the Johns Hopkins Hospital, pregnancy was noted four times in a series of 289 cases at all ages. In going over the records of Lakeside Hospital, but one other instance was noted in a series of over 400 female typhoids, and in this instance the pregnancy was uninterrupted. Thus in 3,608 female typhoids from various sources, pregnancy existed in 93 or less than 3%. But these statistics were collected from cases at all ages and should they be compiled from patients during the childbearing period, the percent would be much higher. The older authors held that pregnancy offered a protection against typhoid, but later observations have not substantiated this claim for in various epidemics in which whole towns were involved, pregnant and non-pregnant women contracted the disease in about the same proportion. On the other hand, Müller has shown that the complications of typhoid are rare in pregnancy and if there is no interruption, the course of the typhoid is apt to be slight. Typhoid usually occurs during the first half of pregnancy and interruption takes place most commonly at the third month and during the second week of the fever. Various causes have been advanced for the frequency of abortion in typhoid, but the mechanism is more complex than is usually supposed and no one theory thus far advanced seems

to hold good for all cases. The experiments of Claude Bernard and Runge furnished the basis that high and prolonged elevation of temperature acted directly upon the fetus and exciting the uterus to contraction with subsequent abortion. Winckel, in Gusserow's clinic, showed that the fetal heart rate increased in direct proportion to the maternal temperature and Gusserow, himself, stated that the danger to the child is proportional to the elevation of the maternal temperature and to the duration of this influence. Abortion occurs in from 50 to 70% of all cases of typhoid. Three causes stand out most prominently: first, high temperature; second, the accumulation of toxins in the maternal blood and their passage through the placenta to the fetus; and third, the death of the fetus. Most writers agree that the death of the fetus is the most common cause of the abortion. In the earlier cases, proof of the transmission of typhoid from the mother to the child was naturally sought in lesions of the intestine similar to those of adults and Charcellay in 1840, and Manzini in 1841, reported cases of fetal typhoid, but these cases were not fetal typhoid as the transmission of the disease can only be ascertained by bacteriological means. For even in children, typhoid is often a bacteriemia and intestinal lesions are wanting. However, the presence of rose spots in the fetus has been noted in a few cases. That the typhoid bacillus is transmitted through the placenta has been shown by many observers. F. W. Lynch at the Johns Hopkins Hospital was able to demonstrate and grow the typhoid organism from the fetal blood and organs in two cases, although in neither did the fetal blood give a positive Widal reaction. Brown and Fordyce, however, have reported cases in which the organism was cultivated from the fetal organs and in which both the maternal and fetal blood gave a positive reaction. Thus it has been definitely proved that the typhoid bacillus can traverse from mother to child through the placenta; that infection of the fetus results, and that intra-uterine typhoid takes place; this, from the first, is a general septicemia and therefore the classical symptoms and intestinal lesions are wanting. The fetus usually dies in utero, or soon after birth, as a direct result of the typhoid infection. It may be born alive but death usually occurs in a few days without definite symptoms. It is also possible that the fetus may pass through an intra-uterine typhoid and be born alive and well, but we have no proof that this happens. Furthermore, infection of

the fetus does not always occur and the pregnant woman does not necessarily transmit the disease to her child.

The history of the case to be reported is as follows:

E. H., female, aged 23, married, was admitted to Lakeside Hospital, August 14, 1905, complaining of headache, fever and pain in the back and joints. Has one child 16 months old, living and well; has not menstruated for past four months. Otherwise the family and previous history are negative. Present illness began August 1, 1905, with headache, general malaise, fever and chilly sensations, also nose-bleed, vomiting, appetite lost and bowels constipated. On physical examination patient proves to be a well nourished woman; rather apathetic; pupils dilated; tongue coated and tremulous; pulse low tension and markedly dicrotic; heart and lungs negative; abdomen full and distended, marked swelling of lower portion and considerable tympanites; a beautiful crop of rose-spots present; spleen not palpable; uterus easily made out on abdominal palpation, soft and enlarged, extending to a point 10 cm. below the umbilicus in the median line. On vaginal examination, cervix soft and the enlarged bulging uterus easily made out. Breasts enlarged and a small amount of colostrum obtained on pressure. No fetal heart sounds heard. Leukocytes 8,700, hemoglobin 74%. Widal reaction very suggestive. From these findings, the diagnosis of typhoid fever, associated with pregnancy, was made. Patient was placed under special enteric precautions with baths at 90° F. if the temperature exceeded 102.5° F. She took water and nourishment well and the temperature began to fall gradually. On August 21, she began to complain of pain in the abdomen and back which simulated labor pains. The ice coil was applied to the abdomen and an opium suppository given which quieted her and the pains ceased. The Widal reaction was now positive. Everything went well until the morning of September 3, when she was attacked with sharp labor pains. These became more severe and at 2 p. m. they occurred at three minute intervals. On examination the cervix was found dilated to about the size of a quarter dollar and membranes bulging. At 3 p. m., membranes ruptured. Patient had been prepared for delivery with rigid aseptic precautions and at 3:45 p. m. a dead fetus was born. Five minutes later, the placenta was expressed by the Credé method. Hemorrhage was slight and patient stood the procedure very well. The cord, placenta and fetus were immediately placed in a sterile dish and transferred to the pathological laboratory. The following report upon them was submitted by Dr David Marine:

Body received in a sterile dish and the dissection was done with aseptic precautions, especial attention being paid to the bacteriology. Placenta measures 11 x 2.5 cm., generally circular in shape, the usual number of lobes present, membranes normal, few clots on maternal surface and on section it is generally gray with many small hemorrhagic areas. Cord normal. Fetus, a male, white child, 24 cm. long, still warm. Extensive extravasation of blood into tissues of scalp, otherwise negative. Abdominal cavity contains about 2 c. c. of clear yellow fluid. Intestines about the size of a slate pencil, and contain a gelatinous fluid. Meconium-like material in sigmoid-colon. Liver fills greater part of abdomen above um-

bilicus, is dark red in color and on section presents no macroscopic lesion. Spleen normal. Lungs pink and airless. Heart normal. Kidneys well formed, 2 cm. long and on section the structure is easily made out. Bladder distended and contains 2 c. c. of a nearly clear fluid. Cultures were taken from the cut ends of the cord, peritoneal and bladder fluids, from the heart's blood, lung, liver, spleen, kidneys and placental blood, using in each case an Ehrlenmeyer flask containing about 75 c. c. of plain bouillon; to this five or eight drops of the fluid or a bit of the tissue was added. This was further supplemented by stroke cultures on slant agar and blood-serum and plates from the various organs and fluids. They were incubated for 17 hours at 27° C., and examined with the following results. In all the media there was found a slightly irregular staining, medium sized and very actively motile bacillus, negative to Gram's stain. Each group of inoculations presented the same cultural characteristics which were: On glucose, a slight growth along stab, no gas. In litmus milk, no change. On potato, growth demonstrable on oblique illumination. In bouillon, slight clouding. On slant agar, fine growth, with serrated margin, glossy; slightly raised on surface, bluish-white and translucent in color. All cultures were examined again at 24 and 48 hours respectively. The single organism, above described, alone growing out, proved to be morphologically and culturally, *Bacillus typhosus*.

To prove conclusively that the organism was the typhoid bacillus, the following agglutination tests were made. A number of serum tubes were taken from the peritoneal fluid and the fetal heart blood. Using the fetal serum and a known typhoid organism, the Widal was suggestive. However, with the peritoneal fluid and a known culture, the Widal was positive instantaneously in a 1-10 dilution and in five minutes in a 1-50 dilution. Using the fetal organism and a known serum from a number of typhoid patients in the ward, the Widal was positive in every instance. Using the fetal organism and the fetal serum, with the heart's blood, the Widal was suggestive, but with the peritoneal fluid, it was immediately positive. Using the fetal organism and the maternal serum gave a positive reaction. The organism which was recovered from the fetus has since been used for agglutination tests in the laboratory. Thus from the serum tests the organism also proved to be the typhoid bacillus.

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THE AIR OF THE OPERATING-ROOM AS A POSSIBLE FACTOR IN THE INFECTION OF WOUNDS.*

BY

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WITH a perfected technic it would be possible to prevent the access of any pathogenic organism into operative wounds. To the attainment of such perfection there are numerous hindrances, but with the majority of these we have been able to cope and avoidable infections are growing every year more rare. Whereas in former times it was taught that all infections were propagated through the air, not a few authorities now state that no pyogenic organism has ever been obtained by culture methods from the air of the operating-room. Personally, I believe that this statement goes too far, as under certain circumstances we have been able to demonstrate their presence.

According to Flügge, the supposition that no germs enter the air from liquids or moistened surfaces holds good only so long as the surface of the liquid remains unmoved and intact. A moderate wind (of a velocity of four meters to the second) suffices to set free germ-containing droplets from the surface of water, moist articles, and the like. In closed apartments droplets are set free more frequently than is generally supposed during sprinkling, washing, manipulating wet linen, and—what is of special importance—during speaking, sneezing, and coughing. These germ-bearing or germ-free droplets, as Flügge has further demonstrated, are carried by the slightest current of air for considerable distances not only in a horizontal, but also in a vertical direction. In order to demonstrate the dissemination of such droplets during speaking, coughing and sneezing, Flügge had the person under observation introduce into his mouth a suspension of *B. prodigiosus*. The tests gave positive results. The plates exposed at a distance of several meters became covered with the characteristic colonies and remained sterile only after quiet speaking in a low tone.

*Read before the American Gynecological Society, April 22, 1909, at New York.

With regard to the dissemination of desiccated germs, naturally only those diseases are transmitted in this way whose exciting agents are capable of surviving in the dried state. Thus Max Neisser (quoted by Harrington) concludes that dust infection is impossible with the organisms of diphtheria, typhoid fever, cholera, plague, and pneumonia, but possible with *Staph. pyog. aureus*, *B. pyocyaneus*, *B. anthracis*, *B. tuberculosis* and *Meningococcus*.

Sternberg says: "If we have on one side of our laboratory a dusty street and on the other a green field, more bacteria will naturally be found when the wind blows from the direction of the street than when it comes from the opposite direction; or if the air is filled with dust we may expect to find many more than when the room has been undisturbed for some time." Graham Smith investigated the air of the House of Commons and found no organisms pathogenic for man and only a few that were pathogenic for animals.

Prof. Wm. H. Welch says: "As compared with contact infection, infection of wounds from the air is of minor importance, but surgeons are not agreed as to whether or not the dangers of air infection are so slight that they need not be taken into consideration at all. At present there is again a tendency to pay more attention to the possibilities of infection from this source and some surgeons have even gone back to the spray." Haegler (quoted by Welch) found staphylococci and streptococci in the majority of his examinations of the air in wards and operating-rooms of the hospital in Basle, and the number of such cocci was in general proportionate to the opportunity for entrance into the air of cocci from dry material and to the amount of dust stirred up by movement in the room. Haegler concludes from his investigations that the danger of infection from the air is greater than is assumed by many surgeons.

Waring, investigating the air of the operating theater and certain wards of St. Bartholomew's Hospital, isolated only two pathogenic organisms—*Staph. pyog. aureus* and *albus*. In Coborn ward, however, into which cases of erysipelas are admitted, he found *Strept. pyogenes*.

Our present research was undertaken in order to find out whether by any special preparation of the operating-room the number of living bacteria that might be present in the air could be minimized. Furthermore, we wanted to find out whether it would be a safe procedure to employ an electric fan in the oper-

ating-room during operations in the hot summer days, since all of us know what a boon this would be, provided that the safety of the patient and the preservation of a good technic would allow of it.

The present report is merely a preliminary one, since, although a great deal of work has been done, the facts at hand as are yet insufficient for the purpose of drawing any definite conclusions.

The technic that we employ in the gynecological service of the Lakeside Hospital in Cleveland in dealing with our operating-rooms immediately before and after an operation is as follows: After an operation the floor, tables, hand basins, and other receptacles are washed with gold dust or Gibson's powder. (If the receptacles are blood-stained they are also washed with Labarraque's solution.) The floor is then washed with soap and water, then with plain water, and finally is mopped dry. On the morning of the operation the floor, woodwork, and all utensils in the room are wiped, and then washed with soap and water. After the floor has been mopped with a 1-1000 bichloride solution, the tables, hand basins, etc., are washed with a 1-20 carbolic acid solution. After everything is in readiness in the operating-room the floors are mopped again with a 1-1000 bichloride solution. It is our rule never to operate knowingly upon a pus case in our main operating-room. Such operations are performed in a special room set aside for this purpose. If we accidentally met with pus during an operation in the main operating-room, no further operations are carried out in this room on that day, and before the room is used again the floor, furniture, and wash-bowls are carefully washed with soap and water and a 1-20 carbolic solution.

In carrying out these experiments we have tried to notice whether the differences in the methods of preparing the room caused any perceptible and constant difference in the number of bacteria falling per minute upon the plates, and to discover whether any pathological forms were present. The general method was to expose during an operation solidified agar-agar plates. In some cases twelve were employed, in others twenty; but the total time of exposure was the same for each series. The plates were incubated for forty-eight hours and the colonies then counted. Later cultures were made from the colonies and the different varieties were identified as far as possible. When a given variety could not be identified, injections were made into guinea-pigs, rabbits, or mice to test for pathogenicity.

The factors taken into consideration were: The condition of the walls and of the floor, and whether the electric fan was or was not running.

The experiments were divided into the following series:

Series A.—The floor was washed with a 1-1000 bichloride solution.

Series B.—The floor was washed with a 1-20 carbolic acid solution.

Series C.—The floor was washed with plain water.

Series D.—No preparation of the floor.

Series E.—Experiments in rooms other than the gynecological operating-room; no preparation of the floor.

In each series one set of plates was exposed while the fan was running and another set when the fan was not running. In our inoculations we used 1 c.c. of a twenty-four-hour (or a forty-eight-hour) bouillon culture, which we injected into the muscles of the back.

RESUME OF EXPERIMENTS.

Series A, No. 1.—Floor washed before operation with a 1-1000 bichloride solution.

In these twelve plates were found eighteen different varieties of bacteria and we were able to identify nine varieties, three others being traced to their groups. The remaining five varieties were tested (by inoculation into white rats) and were found to be nonpathogenic. No pathogenic organisms were found.

On ten of the twelve plates *Bact. rhodochrom*; on six of the twelve plates *Sarcina aurantiaca* was found. All the plates with one exception contained *Sarcina lutea*. On three plates *B. subtilis* was found. Moulds were not very common, one or two occurring on each of five plates of the twelve.

It was observed that the plates exposed near the head of the table contained a great many more bacteria than those exposed at other parts of the room. This is probably due to the fact that there was more motion of the air in that part of the room.

In all of these experiments the average falling on each plate per minute was 4.08. This was determined by counting the total number of colonies on all the plates and dividing this number by the sum of the number of minutes each plate was exposed. Total colonies: $2885 \div 705 \text{ minutes} = 4.08$.

Series A, No. 2.—Floor washed before operation with a 1-1000 bichloride solution, and electric fan set in motion.

The conditions under which these plates were exposed were the same as in series A, No. 1, except that in this case the fan was running, and the plates were exposed toward the close of the operation, *i.e.*, when the wound was being sewn up. No pathogenic bacteria were found. The total number of colonies on all the plates was 2778. Dividing this number by 710, the number of minutes of exposure, and our number of bacteria per minute was 3.9. In the first series without the fan, the number was 4.08. Thus we see that the number of bacteria falling on the plates was slightly less with the fan running. In testing pathogenicity we inoculated guinea-pigs with 1 c.c. of a twenty-four-hour bouillon culture of the bacteria injected under the skin of the back, but obtained no local or general reaction.

Bact. rhodochrom was found on eleven out of twelve plates; *Sarcina lutea* on eleven; moulds on eight plates; *Bact. arborescens* on seven plates; *B. subtilis* on eight plates; *Actinomyces* on eight plates; Nonpathogenic, dot-like, white colonies on eight plates; *B. gemmus* on six plates; *Micrococcus simplex* on eight plates; *Streptococcus mirabilis* on one plate; *M. alvi* on one plate; *B. liquefaciens* on two plates; belonging to *Bact. ambigua* group, one on one plate. The total number of different varieties was thirteen.

*Series B, No. 1.**—The floor of the operating room was washed with a 1-20 carbolic acid solution.

The total number of colonies falling on all the plates was 461. Dividing this by 710, the total time of exposure, we get 0.65 colonies per minute. With the first series of plates the number of colonies per minute was 4.08. The total number of varieties found was twelve and by inoculations into guinea-pigs and white rats we found that all were nonpathogenic. None of the guinea-pigs or rats showed even a local reaction. In this series *Sarcina lutea* was found most commonly, being on all of the twelve plates; *B. subtilis* was found on ten out of twelve; Moulds on ten out of twelve; *Bact. rhodochrom* on five plates; *Micrococcus cumulus* on eight plates out of twelve; *B. proteus vulgaris* on five plates; *Micrococcus citreus* on four plates; *M. simplex* on seven plates.

Series B, No. 2.—Floor washed with a 1-20 carbolic acid solution, fan running.

The conditions under which this series of plates was exposed

*It must be borne in mind that after the use of the bichloride and carbolic acid solutions on the floor enough of the chemicals might be carried with the dust to inhibit the growth of the bacteria that settles on the Petri plates.

were as nearly as possible the same as in the other series. The exposure was begun near the close of the operation, when the wound was being sewn up. The total number of colonies was 1707; the number per minute 2.04. This number is greater per minute than we had in the series when the fan was not running, but it is smaller than in either of the bichloride series.

In this series no pathogenic organisms were found. Our four series seem to show that there are fewer bacteria in the air when carbolic acid is used than when bichloride is employed.

*Series C, No. 1**—No preparation of the floor. Fan not running.

The conditions under which this experiment was performed were about the same as before, twelve plates being used. On account of the fact that no antiseptic was used upon the floor the number of bacteria was much increased, so much so, in fact, that a differentiation into varieties would apparently have been impossible. We therefore decided to expose more plates for a shorter length of time each, but making the total time of exposure the same.

A total of 13,916 colonies fell on the twelve plates in 730 minutes, making 19.6 colonies per minute, many more than in the series in which antiseptics were used upon the floor.

Series C, No. 2.—Nothing on floor. No fan running.

The conditions under which this series of plates were exposed were as nearly as possible the same. The exposure lasted practically through the whole duration of the operation, which, however, was rather short. On account of the large number of colonies which had grown out on twelve plates exposed in Series D, No. 1., we decided to expose a great number of plates, each one for a shorter length of time, but so as to make the sum total of exposure time the same. The total number of colonies was 10,105, the number per minute of exposure being 14.2. As will readily be seen, the number was much greater than when the antiseptic was used upon the floor.

In this series no pathogenic organisms were found.

There were thirteen varieties, numbered from A to M inclusive. Of this number, eight were identified. These five unidentified varieties were tested on guinea-pigs. In no case was there any reaction whatever.

*In the remaining series (as shown by our protocols) in addition to the organisms that have been mentioned the following were found. *M. flavus*, *Staph. albus*, *Bact. fulvum*, *Streptothrix*, *M. candidus*, *B. aureus*, *B. pyocyaneus*, *B. col. commun.*

Series D, No. 1.—Floor cleansed with water after the walls had been cleaned. Fan running.

The conditions under which this series of plates were exposed were inadvertently somewhat different. After the exposure it was learned that some three or four days previously the house-keeper had had the walls and ceiling washed. The floor had been washed with plain water. The fan was running during the entire time of exposure. Here again the number of plates exposed was twenty, the total exposure time being 710 minutes, as in each of the other series. It will be seen that the number of colonies was the smallest found in any series, in spite of the fact that the floor had been cleansed only with water and that the fan was running. The average was .32 colonies per minute.

In this series no pathogenic organisms were found.

There were eleven varieties, numbered (including duplicates) from A to M, inclusive. Of this number six were identified; three were traced to their groups; and two were not identified. Of the doubtful ones, none were pathogenic for guinea-pigs. In no case was there any reaction whatever.

Series D, No. 2.—Floor was not prepared; three weeks previously the walls had been cleaned. Fan running.

The conditions under which this series was exposed was practically the same as for Series E, No. 1, except that a longer period of time had elapsed after the walls had been cleansed. The floor received no preliminary preparation whatever. The fan was running during the entire time of exposure. Here again the total number of plates exposed was twenty, the total exposure time being 710 minutes. The number of colonies falling on the plates per minute of exposure was the smallest with any series up to date. The average was .02 colonies per minute.

In this series no pathogenic organisms were found.

There were only six varieties, and only fourteen colonies on the entire twenty plates. Of the different varieties, two were identified, and four were not. The latter were not pathogenic for guinea-pigs.

Series E, No. 1.—Exposed in pus operating-room. Fan running. Floor with absolutely no preparation. The walls had been cleaned within two or three weeks previously.

In this series twelve plates were exposed, the total time of exposure being the same as for the preceding series, 710 minutes.

The floor had had no special preparation, and for some time

had had no preparation or care except an occasional mopping. The fan was running during the entire time of exposure.

The number of colonies which fell during this time was 105, the average number falling per minute being .15, somewhat more than in the preceding series.

Six varieties of organisms were found, exclusive of moulds. Of these four were identified. The remaining two did not prove pathogenic for guinea-pigs when 1 c.c. of a forty-eight-hour culture was injected under the muscles of the back.

One interesting thing about this series is that *B. pyocyaneus* appeared on one plate, which was exposed under the sink. This organism was typical in every way, but though cultures were injected into the peritoneal cavities of a rabbit and a guinea-pig, no ill effect was noted.

Series E, No. 2.—Exposed on Sunday, February 7, 1909, in different parts of pit in the surgical amphitheater. The walls had not been washed for some months. The floor had had only the ordinary preparation—a mopping with water. Fan running. No operation. Twelve plates exposed. Total exposure time, 710 minutes. Total number of colonies on twelve plates, 2.

Series E, No. 3.—Exposed on Sunday, February 7, 1909, in different parts of pit in the surgical amphitheater. The walls had not been washed for some months. The floor had had only the ordinary preparation—mopping with water. Fan running. No operation and scarcely any movement of air in the room. Twelve plates exposed. Total exposure time 710 minutes. Total number of colonies on twelve plates, 1.

Series E, No. 4.—Exposed in a room in the Pathological Building. Fan running. Absolutely no preparation of the floor. Floor and walls very dirty.

In this series twelve plates were exposed, the total time of exposure being the same as in all the other series, 710 minutes.

They were exposed during an experimental operation on a dog, the operation being a secondary one through an infected wound.

Only three varieties were found. The most numerous could not be identified. They were large bacilli of irregular shape, nonmotile, and of luxuriant growth, evidently a contaminating organism which has often been found in the laboratory. It was not pathogenic for a guinea-pig. The two other forms were isolated. One proved to be *M. candidus*, while the other was a typical colon bacillus. This caused the death of a guinea-pig in less than twenty-four hours after intraperitoneal injection, the

postmortem showing that the cause of death was an acute peritonitis. The organism was grown from the cultures made from the peritoneal cavity.

An interesting feature about this series of plates is the extremely large number of mold colonies, and, considering the dirty room, the small number of bacteria. It is possible that the molds may have killed off the other microorganisms.

The total number of colonies (exclusive of molds) was 141. The average number falling per minute of exposure was .2.

CONCLUSIONS.

1. *Floor*.—When other conditions were the same and a just comparison could be made (Series A to C, inclusive), it would appear that the presence of some antiseptic in the wash-water used upon the floor made a marked difference in the number of bacteria falling on the plates per minute (14.2 and 19.6 colonies per minute with no antiseptic, .65 to 4.08 per minute with some antiseptic on the floor).

2. *Fan*.—Whether the fan made any difference or not it would be hard to say. Comparison of Series A, No. 1, with Series A No. 2, would go to show that it did not, while comparison of Series B, No. 1 and B, No. 2 would tend to show that there was a perceptible difference.

3. *Walls*.—The condition of the walls would seem to make the greatest possible difference. This was discovered accidentally, for at first it had been overlooked. Ordinarily the head nurse in the operating-room takes great pains to have the portable enameled furniture, the floor, and all other accessories in spotless condition, while the dust is allowed to gather on the walls for weeks. On examining Series D, No. 1, we were greatly surprised to find almost no colonies and this in spite of the fact that the floor had been mopped up with only ordinary water and that the fan was running. On investigation, it was found that the housekeeper had had the walls of the room thoroughly scrubbed a few days previously. Further experiments showed that this was a most important factor, for even with the floor absolutely uncared for, and with a fan running, practically no colonies were obtained after the walls had been cleaned (see Series E, No. 1).

4. *People in Room*.—But even with the dirty walls, and with no preparation of the floor, and with the fan running, practically no colonies fell on the plates when they were exposed in a room

RESUME OF PROTOCOLS.

Series No.	Room where exposed	Date exposed	Fan running?	Preparation of floor	Additional remarks on condition of room	No. of plates exposed	Total No. of mins. exposure	Total No. of colonies	Colonies falling per min.
A-1	Gyn. O. R.	April, 08.	No	Bichloride.	12	710	2,855	4.08
A-2	Gyn. O. R.	June, 08.	Yes	Bichloride.	12	710	2,778	3.09
B-1	Gyn. O. R.	July, 08.	No	Carbolic	12	710	401	.65
B-2	Gyn. O. R.	July, 08.	Yes	Carbolic	12	710	1,707	2.04
C-1	Gyn. O. R.	Dec., 08.	No	No antiseptic on floor.	12	710	13,916	19.6
C-2	Gyn. O. R.	Dec., 08.	No	No antiseptic on floor.	20	710	10,105	14.2
D-1	Gyn. O. R.	Jan., 09.	Yes	Plain water on floor	Walls cleaned a few days before.	20	710	232	.32
D-2	Gyn. O. R.	Jan., 09.	Yes	No preparation of floor, not even water.	About 3 weeks after cleaning of walls.	20	710	14	.02
E-1	Pus Operating room	Feb., 09.	Yes	No preparation of floor, not even water.	About 2 weeks after cleaning of walls.	12	710	105	.15
E-2	Amphitheater	Feb., 09.	No	No preparation of floor	Walls not cleaned for months, but <i>no one</i> in room.	12	710	2	.002
E-3	Amphitheater	Feb., 09.	Yes	No preparation of floor.	Walls not cleaned for months, but <i>no one</i> in room.	12	710	1	.001
E-4	During oper. on dog in Dr. Robb's room in Path. Bldg.	Feb., 09.	Yes	No preparation whatever.	Walls and floor very dirty.	12	710	141	.2

RESUME OF PROTOCOLS.

Series No.	No. of Colonies on each plate.*																				No. of moulds	No. of pathog. varieties	Total No. of varieties	No. of varieties ident.	No. of varieties not ident.	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20						
A-1	(105) 70	(45) 40	(85) 106	(55) 12	(20) 4	(65) 25	(40) 18	(35) 1384	(55) 438	(45) 317	(120) 220	(40) 220										5	0	18	9	9
A-2	(105) 11	(45) 175	(85) 32	(55) 105	(20) 45	(65) 1531	(40) 332	(35) 160	(55) 274	(45) 38	(120) 68	(40) 48										23	0	13	8	5
B-1	(105) 65	(45) 44	(85) 53	(55) 45	(20) 23	(65) 48	(40) 39	(35) 21	(55) 25	(45) 51	(120) 28	(40) 19										18	0	12	7	5
B-2	(105) 79	(45) 68	(85) 134	(55) 102	(20) 60	(65) 504	(40) 147	(35) 148	(55) 95	(45) 110	(120) 107	(40) 63										16	0	15	11	4
C-1	(105) 1804	(45) 1169	(85) 1405	(55) 1107	(20) 1619	(65) 112	(40) 1016	(35) 1009	(55) 1263	(45) 839	(120) 1344	(40) 969	(20) 88	(20) 449	(45) 389	(45) 473	(45) 756	(45) 527	(45) 539	(50) 639		2	0	13	8	5
C-2	(30) 656	(30) 249	(30) 713	(20) 520	(20) 547	(20) 636	(25) 262	(44) 569	(44) 518	(44) 525	(44) 496	(44) 544									Not worked out on a separate plate.					
D-1	(30) 8	(30) 15	(30) 15	(20) 5	(20) 1	(20) 5	(25) 5	(44) 27	(44) 12	(44) 20	(44) 11	(44) 15	(20) 2	(20) 7	(45) 35	(45) 12	(45) 16	(45) 16	(45) 19	(50) 19		0	0	11	6	5
D-2	(30) 2	(30) 1	(30) 2	(20) 0	(20) 0	(20) 4	(25) 1	(44) 0	(44) 0	(44) 0	(44) 0	(44) 0	(20) 0	(20) 0	(45) 1	(45) 2	(45) 0	(45) 1	(45) 0	(50) 0		0	0	6	2	4
E-1	(105) 0	(45) 0	(85) 0	(55) 1	(35) 0	(50) 25	(40) 5	(35) 0	(55) 0	(45) 0	(120) 54	(40) 22										2	1?	6	4	2
E-2	0	0	0	0	0	0	1	0	1	0	0	0										0				
E-3	1	0	0	0	0	0	0	0	0	0	0	0										0				
E-4	(60) 0	(60) 9	(60) 13	(60) 8	(60) 0	(60) 11	(60) 16	(60) 24	(60) 37	(60) 6	(60) 3	(50) 8										1		3	2	1

*First No. = No. mins. plate exposed.

on Sunday, when no one was stirring around (see Series E, Nos. 1, 2, 3).¹

5. The finding of *B. pyocyaneus* in a room in which a case infected with this organism had been operated upon three weeks previously is of interest (see Series E, No. 1).

6. The series exposed in the uncared for pathological laboratory should be noted. Here the molds prevailed and there were not many bacteria, but *B. coli* was found. This was the only organism in the entire group which was pathogenic for the laboratory animals.

7. In the summer season when the windows are more or less open the number of bacteria present seem to be more numerous than in the winter season or when the windows are closed.

From our experience from a bacteriological analysis of the air of the operating-room (prepared in the way that we have described) and from our practical experience now in a considerable number of abdominal and plastic operations both on dogs and human beings the electric fan can be kept running during an operation without causing any bacterial infection in the wound. Further experiments, however, from this standpoint will be necessary before positive deductions can be drawn. Thus far the work done seems only to emphasize what we knew before, namely, that an aseptic technic is the necessity of paramount importance.

I wish to express my obligations to Mr. Samuel M. Glenn and Mr. Harold O. Ruh, of the Bacteriological Laboratory of the Western Reserve University, and to Dr. Clyde Cummer, of the Medical Department of the Lakeside Hospital, for the detailed bacteriological work connected with this research.²

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¹ This experiment would strongly support the idea that contamination of the wounds in the operating-room depends mainly upon faults in technic.

² In working out varieties of organisms Chester's Determinative Bacteriology was followed.

PART 2
PATHOLOGICAL AND EXPERIMENTAL
PAPERS

THE MECHANISM OF HÆMOLYSIS WITH SPECIAL REFERENCE TO THE RELATIONS OF ELECTROLYTES TO CELLS

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(Received for publication March 26, 1909)

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INTRODUCTION

An enormous literature has gathered about the important subject of hæmolysis, but comparatively little attention has been given to the intimate mechanism of the process. It is, of course, of interest and importance to know that the serum of an animal of given species will lase the corpuscles of an animal of another given species; that a hæmolytic power not normally present in a given serum can be con-

ferred on it by immunization of the animal with alien corpuscles; that in some diseases the serum becomes lytic to its own corpuscles or to the corpuscles of the normal animal; that a great number of chemical substances will lase the erythrocytes of any animal, and so on. But it is not less interesting to inquire what happens in the erythrocyte under the influence of any hæmolytic agent when it is laked; why does the blood pigment pass out of it; what is the condition of the remainder of the corpuscle after it has lost its hæmoglobin; and very specially, whether the process is the same in all kinds of laking? This last inquiry has been surprisingly neglected. The tacit assumption has been made by the majority of writers that hæmolysis is hæmolysis however it is produced. To take one instance, it is curious to observe how it has been assumed by writers who have investigated the chemistry of the stromata that it is a matter of no consequence whether the blood-pigment has been got rid of by freezing and thawing, by grinding up the corpuscles with sand, by the copious addition of water, or by the action of ether and similar substances. Recently there have been symptoms that the mechanism of hæmolysis has excited more attention.

Liebermann¹ has brought forward evidence that in several forms of hæmolysis ("neutral guaiac saponin," soaps) the determining factor is the formation of a compound between stroma constituents and the hæmolytic substance.

G. Bayer² believes that the lecithin of the erythrocyte membrane is changed into a water-soluble condition by the bile-salts, and that in consequence of this the hæmoglobin escapes. Proteins, according to him, may also be rendered soluble by bile salts.

Neuberg and Rosenberg³ and Neuberg and Reicher⁴ lay stress on the lipolytic power of certain agglutinating substances (croton, ricin) and of certain hæmolysins (cobra, crotalus, moccasin venom) and suggest that a lysis of lipid constituents of the corpuscles is the fundamental change. They state that the lipolytic splitting of lecithin takes place under the action of many hæmolytic agents. This may explain the

¹ Bio-chem. Zeit. iv, p. 25, 1907; xiii, p. 363, 1908; Archiv für Hygiene, lxii, p. 339.

² Bio-chem. Zeit., v, p. 368, 1907; ix, p. 58, 1908; xiii, p. 234, 1908.

³ Berl. klin. Woch. ii, Jan., 1907.

⁴ Bio-chem. Zeit., iv, p. 281, 1907.

permeability of artificial lipid membranes for proferments observed by Swart⁵ or there may be adsorption, without splitting, of lipid.⁶

Arrhenius⁷ explains agglutination by acids as due to coagulation of proteins in the envelope.. The entrance of acids into the corpuscles and therefore their hæmolyzing power is accelerated by lecithin. But he gives no satisfactory explanation of how this is brought about.

Baumgarten⁸ restates his "osmological" explanation of hæmolysis. He finds the fundamental cause of the liberation of the blood-pigment in an altered permeability of the stroma. He correctly distinguishes between total destruction of the corpuscle and liberation of the hæmoglobin. Up to a certain point his ideas coincide with those expressed in my first paper ten years ago, and repeated and emphasized in several succeeding ones. In essential points also my long-published views do not seem to differ fundamentally from some of those more recently put forward by Koepe, Liebermann, and K. Meyer. Meyer⁹ examined the mechanism of saponin hæmolysis. He states that the first experiments on the mechanism of saponin-laking were undertaken by Ransom¹⁰ Two years earlier I published experiments¹¹ on this subject, in which by physico-chemical methods it was demonstrated that a change in the permeability of the corpuscles to electrolytes and water is an essential part of the saponin action. Later¹² it was shown that the action on the permeability of the corpuscles as regards ions still took place when they had been fixed by formaldehyde, and that the constituent on which the saponin acted might therefore be assumed to be non-protein. Ransom's valuable investigation concerns the constituent attacked. He says it is cholesterin. My experiments concern the immediate physico-chemical results of the attack and the way in which those physico-chemical changes lead to the liberation of blood-pigment. Meyer¹³ denies that Ransom's experiments prove that cholesterin is the point of attack. He concludes, himself, that the action of saponin on the lecithin of the corpuscles is the important thing.¹⁴

⁵ Bio-chem. Zeit., vi, p. 358, 1907.

⁶ Dauwe: Hofmeister's Beitr. vi, p. 426, 1905.

⁷ Bio-chem. Zeit., xi, p. 161, 1908.

⁸ Bio-chem. Zeit., xi, p. 21, 1908.

⁹ Hofmeister's Beitr. xi, p. 357, 1908.

¹⁰ Deutsch. med. Woch., xxvii, p. 194, 1901.

¹¹ Journ. of Physiol. xxiv, p. 224, 1899.

¹² Ibid., xxvi, p. 470, 1901.

¹³ Archiv für Hygiene, lxx, p. 293, 1908.

¹⁴ Cf. Pascucci: Hofmeister's Beitr. vi, p. 543, 1905, and Porges and Neubauer: Wien. klin. Woch., p. 1285, 1907; Bio-chem. Zeit., vii, p. 152, 1908.

Koepppe¹⁵ has attempted to explain the various kinds of hæmolysis as the result of simple chemical and physical changes in the envelope of the corpuscle. The appearance of novelty in these conclusions is partly obtained by his ignoring the results of previous workers. On the whole also his explanations are too "simple." For example, heat-laking is due, he says, really following Hermann,¹⁶ to the melting of the fatty substances in the wall of the corpuscle when the temperature corresponding to their melting point is reached. This does not explain why in cautious heat-laking the stromata still contain the greater part of their electrolytes, whereas, in saponin-laking the electrolytes leave the stromata in relatively large amounts. Nor does it explain why electrolytes can be brought out of the ghosts of heat-laked blood by saponin, a substance which is believed to act on the corpuscles in virtue of its power of dissolving lipoids, and to an equal extent by water, which must affect the corpuscles in a different way. Again, Koepppe's explanation of heat-laking takes no account of the fact that although ether and saponin greatly increase the conductivity of formaldehyde-fixed corpuscles by acting on the lipoids, heating formaldehyde corpuscles to the temperature of heat-laking does not increase the conductivity of the suspension, but may even slightly diminish it just as in normal blood.¹⁷ Further, the temperature at which heat-laking occurs is not a perfectly definite temperature, but depends both on the duration of the heating and on the condition of the corpuscles. The rapidity and completeness of heat-laking also depend on the nature and the concentration of the suspending liquid. For instance, cane sugar delays laking although it does not prevent it.¹⁸ These observations have been confirmed by Gros.¹⁹

Peskind²⁰ has carefully investigated the mechanism of ether-laking and sums up "in favor of the hypothesis that the cause of ether-laking is the solution and extraction of cholesterin and lecithin from the envelopes of the corpuscles." "Yet," he cautiously adds, "a more extended research may show that it is only the modification of these substances by ether and not their solution that is the cause." For he found that ether saturated with cholesterin caused laking in the same strength as ether itself.

¹⁵ Pfüger's Archiv, xcix, p. 33, 1903.

¹⁶ Pfüger's Archiv, lxxiv, p. 164, 1899; xci, p. 164, 1902.

¹⁷ Stewart: Journ. of Med. Research, viii, p. 307, 1902.

¹⁸ Ibid., p. 285.

¹⁹ Archiv für exp. Path. und Pharm., lvii, p. 64.

²⁰ Amer. Journ. of Physiology xii, p. 184, 1904.

Bang²¹ repeated Peskind's experiment with the same result, although he does not mention Peskind's work in his extensive article. Bang showed also that ether saturated with lecithin and cholesterin caused laking as rapidly as ordinary ether. He therefore asserts that neither lecithin nor cholesterin is the substance affected by ether in ether-laking. This reasoning is not conclusive. For some ether might be expected to be taken up by the surface of the corpuscles by adsorption²² or distributed over the lecithin and cholesterin of the envelopes in accordance with the partition-coefficient, some of the lecithin and cholesterin in the external ethereal solution being precipitated. Thus, as Peskind pointed out, even although no lecithin or cholesterin might be actually removed from the corpuscle, the condition of the envelope might be altered so that it became more permeable to water and electrolytes. Some ether might be expected also to penetrate to the interior of the corpuscle. Arrhenius²³ has shown how great the concentration of hæmolytic substances in the corpuscles may be in comparison with the surrounding liquid, saponin, for example, when equilibrium is established, having a concentration 120 times greater, and ammonia a concentration 880 times greater in the corpuscles than in the liquid. In this connection, the idea developed by J. Traube²⁴ of the relation between surface tension and hæmolysis is interesting. Starting from the theory of Willard Gibbs, that substances which diminish the surface tension of the solution strive to wander into the surface so that the concentration of such substances in the surface layer becomes greater than in the interior of the liquid, he shows that if we bring a watery phase together with solid phases, as blood cells or bacteria, or together with another liquid, for example, a lipoid solution, the substances which diminish the surface tension of the water most will collect in greatest

²¹ *Ergeb. der Physiol. Jahrg.*, vi, p. 183, 1907.

²² The term "adsorption" is not always used in physiological writings in a perfectly definite sense. Freundlich considers adsorption to be a process of (physical) condensation of the adsorbed substance upon the surface of the adsorbent. (See paper by L. L. and D. D. Van Slyke: *Journal of Bio-chemistry*, iv, p. 259, 1908.) But many writers use the term also for processes not always understood and which seem to include certain chemical reactions. Perhaps "mechanical adsorption" might be advantageously employed (as by Michaelis and Rona: *Bio-chem. Zeit.*, xv, p. 196, 1908) to distinguish the physical process.

²³ *Bio-chem. Zeit.*, xi, p. 161, 1908.

²⁴ *Bio-chem. Zeit.*, x, p. 371, 1908; *Pflüger's Archiv*, cv, pp. 541, 559, 1904; Traube and Blumenthal: *Archiv für exp. Path. und Ther.*, xxii, p. 117, 1906; Traube and Bickel: *Deutsch. Med. Woch.*, p. 28, 1905.

concentration on the surface of the foreign phase, and therefore tend to be adsorbed as well as dissolved to the greatest extent in the foreign phase. Such substances as ordinary alcohols, esters, ethers, ketones, also substances like saponin and bile-acids must for this reason pass from physiological salt solution into the lipid envelopes of the blood corpuscles.

Noguchi²⁵ has pointed out the similarity of the lipolytic form of hæmolysis to the ordinary amboceptor-complement hæmolysis.

Von Dungern and Coca²⁶ attribute the hæmolytic action of cobra venom solely to a lipolytic ferment, and, like Bang,²⁷ deny the existence of compounds between lecithin and cobra toxin (toxolecithids) such as those described by Kyes²⁸ who, however, has ably defended his position.²⁹

Dautwitz and Landsteiner³⁰ see in hæmolysis by sera and toxins, as the essential change, a rupture of the combination of protein and fat-like substances on which the integrity of the cell depends.³¹

I have long been convinced that the mechanism of hæmolysis can only be thoroughly understood when we understand the physico-chemical properties of the erythrocytes and the relation of these properties to their histological structure. A study of the erythrocytes in this regard, besides being of interest in itself, is calculated to throw light upon the relations of the electrolytes of the cells in general to the colloids and to that complex which we call protoplasm, relations which constitute one, or rather a group of the most important problems of physiology and pathology. There is every reason to believe that these relations are intimately concerned in the maintenance of the normal osmotic equilibrium of the cells and liquids and, therefore, in all physiological processes which depend upon the preservation, and in all pathological processes which depend upon the upsetting of that equilibrium. In particular, we may mention as of interest in this connection, such physiological processes as secretion, absorption, the contraction of muscle, the conduction of nerve impulses and, possibly,

²⁵ Bio-chem. Zeit., vi, p. 185, 1907.

²⁶ Ibid., xii, p. 407, 1908.

²⁷ Ibid., xi, p. 520, 1908.

²⁸ Berl. klin. Woch. Nos. 42 and 43, 1903.

²⁹ Ibid., iv, p. 99, 1907.

³⁰ Hofmeister's Beitr. ix, p. 431, 1907.

³¹ Cf. Landsteiner and Jagic: Wien. klin. Woch., 1904; Münch. Med. Woch., 1904.

fertilization and growth³² and such pathological processes as œdema and hæmolysis. How the electrolytes of the plasma of blood and lymph are related to the proteins of these liquids, how and to what extent they pass into the cells, in what physical or chemical conditions they exist in the intracellular contents, what consequences follow the increase or diminution of normal electrolytes or the introduction of abnormal ones, what the regulatory mechanisms are which provide against variations beyond the physiological limits, all these are questions of great interest. None of them, I venture to think, have been exhausted, despite the large amount of attention they have excited in recent years.

The blood and lymph corpuscles have this peculiarity among cells that their whole surface is in contact with a liquid of uniform chemical composition and uniform molecular concentration. Although this is not the case for the whole of the blood or lymph, we can certainly assume that it is so for the small portion surrounding a single corpuscle, moving freely in the blood stream. It may be far from true, however, for a corpuscle which clings for a time to the walls of a capillary through which an active exchange of material is going on. Such a corpuscle may be in some respects in the position of a corpuscle at the edge of a drop of blood on a slide, which may lake even before any visible drying occurs. Other cells, such as glandular epithelium, are very differently situated. The basal surface of a gland cell is in contact with lymph and the alveolar surface with the secretion of the gland. The epithelial cells of the intestine are in a similar position. Their free ends are in contact with the contents of the gut, their deep ends with lymph. Whether or not we consider the envelopes of cells as related to precipitation membranes³³ in which are concentrated certain constituents of the liquid phase with which they are in contact, or which they enclose, or as surfaces of separation between a solid and a liquid phase in which substances that diminish the surface tension collect,³⁴ there can be no doubt that their properties must depend to some extent

³² J. Loeb: *Pflüger's Archiv*, lxxxviii, p. 68, 1901; *Amer. Journ. of Physiol.*, vi, p. 411, 1902; *Bio-chem. Zeit.*, v, p. 351, 1907; etc. Cf. A. P. Mathews, *Amer Journ. of Physiol.* xviii, p. 89, 1907.

³³ Zangger: *Ergebnisse der Physiologie*, Jahrg., vii, p. 98, 1908.

³⁴ Traube: *Loc. cit.*

on the liquids with which they are normally in contact. So that it is not permissible to speak of the permeability of, say, the epithelium of the convoluted tubules as a property constant, under given conditions and for a given substance, for the whole periphery of the cell. For the mammalian colored corpuscles, the boundary which separates the homogeneous intracorpuseular contents from the homogeneous plasma may be considered as possessing a uniform permeability throughout its whole extent. But the kinds of cells for which this assumption can be made are few. Even in the nucleated erythrocytes there are indications that absolute uniformity does not exist unless, perhaps, at points symmetrically placed with reference to the nucleus.

For example, in the action of various laking agents on the colored corpuscles of *Necturus*, it may be seen that the poles of the corpuscle farthest from the nucleus are first attacked. And when swelling of the nucleus is caused by treating sublimate-fixed corpuscles in certain ways, the corpuscles do not yield symmetrically to the swelling nucleus. In the leucocytes the differentiation of internal structure probably carries with it a still greater lack of uniformity in the permeability of the periphery at various points. The same seems to be true of striated muscle fibers, the permeability of which for certain ions appears to be greater at the end attached to the tendon than elsewhere.

The so-called irreciprocal permeability of frog's skin³⁵ and of intestinal mucosa³⁶ are probably illustrations of this. It is not absolutely necessary to assume that in the latter case the phenomenon depends on the presence of two histological layers in the membrane, as Hamburger has suggested. The two surfaces of the epithelial cells must of themselves constitute such a double membrane. Even a double membrane of parchment paper-collodion shows irreciprocal permeability, pepsin passing more easily in the direction from parchment to collodion, water more easily in the opposite direction.

I have already published a considerable number of papers on certain aspects of several of these questions, and promised³⁷ to discuss in detail in a future communication the *modus operandi* of the various

³⁵ Bayliss: *Bio-chem. Zeit.* xi, p. 226, 1908.

³⁶ Hamburger: *Ibid.*, p. 443, 1908.

³⁷ *Amer. Journ. of Physiology*, viii, p. 103, 1902.

hæmolytic agents investigated. I now desire to redeem this promise by bringing together, as far as possible, in a general view the deductions which seem to follow from my own observations, comparing and supplementing them with results obtained by others.

The investigation of certain physico-chemical properties of the corpuscles and their relation to the structure of these cells will constitute the first half of this paper, the second half being occupied more specifically with the mechanism of hæmolysis. But this division is merely for convenience in the treatment of what is after all a single theme, and matters which formally belong to one division may not infrequently be referred to in the other.

PART I. CERTAIN PHYSICO-CHEMICAL PROPERTIES OF ERYTHROCYTES AND THEIR RELATION TO THE HISTOLOGICAL STRUCTURE OF THESE CELLS

Historical Note.—The fundamental fact that the colored corpuscles are practically non-conductors was first observed by me in an investigation on the output of the heart, by a method involving the measurement of the conductivity of numerous samples of blood before and after the injection of sodium chloride solution into the left ventricle. The first communication was presented to the American Physiological Society in December, 1896.³⁸

A more particular account of the phenomenon was published in the *Journal of the Boston Society of Medical Sciences* No. 16, June 15, 1897. The paper was dated June 3. I there stated

1. That the electrical resistance of defibrinated blood is from two to five times greater than that of the serum.
2. That when defibrinated blood is centrifuged and samples taken from different portions of the tube, the resistance increases with the proportion of corpuscles in the sample. The resistance of a sample from the bottom of the tube may be fifteen times that of the serum or even more.
3. Since in such sediments there is always some serum between the corpuscles the conclusion seems warranted that in comparison with the serum the blood corpuscles are non-conductors.

Thus, a sediment with conductivity only $\frac{1}{16.5}$ of that of the serum still contained 12 per cent of serum by volume. Could this have been all

³⁸ *Science*, Jan. 22, 1897.

removed, the conductivity would have been enormously less. In another experiment³⁹ a sediment had the conductivity of 3.88 the serum 86.22, the defibrinated blood 29.48. That is, the conductivity of the sediment was only $\frac{1}{22}$ of that of the serum, although the sediment still contained 7.7 per cent of serum. Bugarsky and Tangl obtained sediments with a conductivity only $\frac{1}{30}$ of that of the serum, and these of course were still admixtures of serum and corpuscles.

In discussing the meaning of this remarkable fact, I pointed out that two explanations suggest themselves.

(a) That the corpuscles, while containing dissociated ions and therefore capable of electrolytic conduction in their interior, are surrounded by a non-conducting envelope—an envelope, let us say, which refuses passage to the ions that exist in the blood, but not necessarily an envelope structurally differentiated from the rest of the corpuscle.

(b) That throughout the whole substance of the corpuscle the bodies (inorganic salts) which would otherwise behave as electrolytes are combined with non-conducting, non-dissociable molecules, (hæmoglobin and other proteins,) and thus rendered for the time non-dissociable.

In attempting to decide between these two explanations, I quoted the results of experiments on laking the blood in various ways, some of which seemed consistent with either explanation, but others consistent only with the second. For example, when blood is rendered laky by repeated careful freezing and thawing, the resistance is not in general lessened, but may be somewhat increased; but if distilled water be now added to the already laked blood, the resistance (allowing for the dilution) is diminished just as if the water had been originally added to unlaked blood. This seemed to show that not only may the inorganic salts of the corpuscles be bound in non-dissociable combinations within the intact corpuscles, but that those combinations, or some of them, can exist even after the corpuscles have been laked so long as they are not exposed to the dissociating influence of dilution. It was pointed out that the stability of the quantitative and even qualitative differences in the easily diffusible inorganic constituents not only between the blood corpuscles and plasma, but between the organized material and the liquid of the tissues in general seems to require some such theory for its explanation.

About a month later W. Roth⁴⁰ announced that the conductivity of

³⁹ Journ. of Med. Research, viii, p. 305, 1902.

⁴⁰ Centralblatt für Physiologie, xi, July 10, 1897.

the red corpuscles was so small that they could be considered non-conductors. I thereupon called attention to my results,⁴¹ giving specimens of the numerical data and indicating how the phenomenon in question might be used to determine the relative volume of plasma and corpuscles without the more or less artificial changes entailed by other methods, such as the hæmatocite method even when the admixture of salt solutions is avoided.

The statement of L. Löhner in a recent paper⁴² that Burgarsky and Tangl first showed that the red corpuscles are bad conductors is incorrect.⁴³

Pursuing the subject, I presented⁴⁴ certain facts which showed that the still relatively high resistance of blood laked by gentle means (careful freezing and thawing, careful heating to 60° C., foreign serum, spontaneous laking) was not due to the liberation of the electrolytes of the corpuscles in such a form that they could not conduct, since the addition of the more violent laking agents (water, supraminimal doses of saponin) to the sediment of the laked blood containing the ghosts caused a marked increase in the conductivity, while their addition to the serum of the laked blood caused a much smaller relative increase in conductivity, an increase similar to that obtained in normal serum.

Oker Blom, applying the same methods⁴⁵ but without reference to my work, published a paper containing tables and curves showing a striking similarity to mine. In subsequent work⁴⁶ he obtained further confirmation of my results, amplifying them in certain points.

Condition of the intracorpuseular electrolytes. These experiments, then, while they did not disprove the idea that the cause of the low conductivity of the corpuscles is the existence of the electrolytes in them in such a condition that they cannot conduct, lent it no support because they failed to discover evidence of the liberation of such compounds when the hæmoglobin escapes from the corpuscles in the act of laking. In short, the net result of the work up to this point as regards the question we are discussing, was to throw back the inquiry

⁴¹ Ibid., August 7, 1897.

⁴² Pfüger's Archiv, cxx, p. 193, 1907.

⁴³ Bugarsky's paper was published in the Centralblatt für Physiologie, July 24, 1897.

⁴⁴ Journ. of Physiol., xxiv, p. 211, 1899.

⁴⁵ Pfüger's Archiv, lxxix, p. 111, 1900.

⁴⁶ Ibid., lxxix, p. 510; lxxxi, p. 167, 1900.

from the intact corpuscle to the shadow. This statement is based on such evidence as the following obtained with several methods of laking.

Spontaneous Laking. 1. The extracorporeal liquid of dog's defibrinated blood which had been laked by standing eight days at room temperature, was filtered free from ghosts. It still contained the hæmoglobin in solution. The conductivity of the liquid, when corrected for the depressing influence of the hæmoglobin,⁴⁷ was of the same order of magnitude as that of dog's serum, while the conductivity of the laked blood was of the order of magnitude of that of dog's defibrinated blood, the relation between the two being 3.6 : 1. On diluting the filtrate with water, the relative increase of conductivity was only as much as occurs in the case of normal serum.

2. When two suspensions of corpuscles in serum, the one rich and other poor in corpuscles, undergo spontaneous laking under the same conditions, the conductivity of the second suspension, when laking is complete, is many times greater than that of the first. The conductivities are of the same order of magnitude as those of suspensions rich and poor respectively, in intact corpuscles. The addition of water or saponin causes a relatively great increase in the conductivity of sediments rich in ghosts and a relatively small increase in conductivity of suspensions poor in ghosts. The conclusion is, therefore, warranted that the ghosts in parting with their hæmoglobin have not in this form of laking parted with any large proportion of their electrolytes. They remain relatively bad conductors not because they have lost their electrolytes but because their relation to electrolytes, both their own and those of the serum, remains the same as that of the intact corpuscles notwithstanding the discharge of the hæmoglobin.

Heat-laking. With cautious heat-laking a similar result is obtained.

⁴⁷ Hæmoglobin, like other non-conductors, depresses the conductivity of a solution of electrolytes (in the case of serum, by 1.88 per cent for each gram of dog's oxy-hæmoglobin dissolved in 100 cc. of serum.) I stated long ago (Studies from Physiol. Laboratory, Owen's College, Manchester, p. 144, 1890) that when oxyhæmoglobin is dissolved in distilled water there is no convection of it under the influence of a voltaic current. Pauli (Hofmeister's Beitr., vii, p. 531, 1906) has recently shown that the same is true for the serum proteins freed from electrolytes by dialysis. Like other colloids, oxyhæmoglobin exhibits electrical convection when it acquires a charge in solutions of electrolytes (Gamgee: Proc. Roy. Soc. lxx. p. 79, 1902.)

The extracorporeal liquid, freed from ghosts, has a conductivity of the same order of magnitude as that of the blood serum while the conductivity of the sediment is much less. Dilution with water produces a much greater relative increase in the conductivity of the sediment than of the liquid. Therefore, the influence of water in increasing the conductivity of heat-laked blood, is exerted mainly on the ghosts and not on the extracorporeal liquid. The increase of conductivity produced by saponin in heat-laked blood can in like manner be shown to be due to an action on the ghosts.

Saponin. The following facts show that the increase of conductivity produced by saponin (or sapotoxin), in the case of fresh blood, is not due to the breaking up of protein-salt compounds in the extracorporeal liquid:

1. Saponin does not produce such an effect on serum.
2. When saponin acts on defibrinated blood at 0° C. a stage can be found, when the dose of saponin is not too great, in which the conductivity is increasing while as yet no hæmoglobin has escaped from the corpuscles. The increase in conductivity, of course, cannot be due to decomposition of combinations of electrolytes in the serum. It is probably due to increased permeability of the corpuscles to ions, but possibly to some extent to enrichment of the serum with corpuscular electrolytes. As soon as the exit of hæmoglobin begins, the conductivity falls somewhat (depressing influence of the hæmoglobin as a non-conductor) and goes on falling until all the hæmoglobin is liberated, if the dose is no larger than suffices to cause its complete liberation. With a larger dose the first stage of increased conductivity is still seen and also the stage of decreased conductivity. But the latter does not go so far and is succeeded during the exit of the last portion of the hæmoglobin by an increase of conductivity (due to escape of electrolytes and diminution of the mechanical effect of the corpuscles on the conductivity). With still larger doses⁴⁸ the second stage of diminished conductivity may be absent or very slightly marked. Here the depressing influence of the hæmoglobin is overcome by the liberation of electrolytes from the start.

It is a remarkable circumstance that when the saponin acts at

⁴⁸ Experiment iv, Amer. Journ. of Physiol., ix, p. 87, 1903.

0° on washed corpuscles⁴⁹ suspended in saline instead of on defibrinated blood, the stage of increased conductivity is either absent or is so short that practically, with minimal doses of saponin, the conductivity goes on diminishing steadily so long as hæmoglobin is liberated. In experiment VI⁵⁰ with a large dose of saponin acting on washed corpuscles, no stage of diminished conductivity can be detected. The saponin causes a marked increase in conductivity, whereas in the same suspension with a small dose the stage of diminished conductivity is very distinct, not being preceded, however, by a stage of increased conductivity. The most probable explanation of these differences is that a serum constituent (in the case of defibrinated blood) which combines with or dissolves saponin (cholesterin?) hands it over slowly to the corpuscles, or is itself taken up by the envelope and continues there to protect the corpuscle, so that the first stage of increased permeability without liberation of the hæmoglobin is brought about. The envelope alone being affected, the combination between the blood-pigment and the stroma is not loosened at this stage. Or it may be that such effect as is produced on the envelope is only great enough to allow ions to pass through but not yet hæmoglobin. A similar phenomenon is seen in the case of bile salts acting at 0°, although the preliminary increase of conductivity is less marked.⁵¹

3. The conductivity of the extracorporeal liquid after laking with saponin is not increased, allowance being made for the depressing influence of hæmoglobin, but that of the sediment is greatly increased⁵²

4. The conductivity of the extracorporeal liquid after saponin has acted on formaldehyde-fixed corpuscles is such that we must conclude that the increase of conductivity of the suspension is due to an increase of conductivity in the corpuscles and not in the extracorporeal liquid.

That saponin produces its effect on the conductivity of blood in the same way whether the blood is fixed by formaldehyde or is fresh is indicated by the following facts:

1. When blood is gradually fixed by formaldehyde and acted on by

⁴⁹ Experiment vii, *Ibid.*, p. 91.

⁵⁰ *Ibid.*, p. 89.

⁵¹ *Ibid.*, p. 93.

⁵² *Journal of Experimental Medicine*, vi, p. 275, 1902.

saponin from time to time, the percentage increase of conductivity produced by a given dose of saponin is the same whether laking occurs or not.⁵³ This is especially true when such doses of saponin are used as suffice to produce complete laking in unfixed blood. When smaller doses are used, the depressing influence of the liberated hæmoglobin on the conductivity of the extracorporeal liquid may mask the increased conductivity of the partially laked corpuscles or the ghosts and cause the conductivity of the unfixed blood to undergo a smaller alteration under the influence of saponin than the fixed blood.

2. When the percentage increase in conductivity produced by a given dose of saponin on unfixed blood is compared with that produced on fixed blood, the effect is found to be approximately the same, provided that allowance is made for the depressing influence of the hæmoglobin.

How does saponin increase the conductivity of the corpuscles? There are three possibilities: (a) by increasing the permeability of the corpuscles to the ions of the suspending liquid; (b) by increasing the dissociation of ions inside the corpuscle; (c) by increasing the permeability of the corpuscles to intracorporeal ions. Granted that (a) takes place, the conductivity of the corpuscles may be greatly increased by (b) and (c). If (b) alone occurs without (a) or (c) no effect can be produced on the conductivity either of corpuscles or suspending liquid.

If (b) and (c) happen without (a), the conductivity of the suspending liquid and, therefore, the conductivity of the suspension would be increased by the enrichment of the liquid with intracorporeal electrolytes while the corpuscles remain non-conductors.

In the case of saponin acting on formaldehyde corpuscles (a) must be assumed to have taken place, since when a suspension is treated with saponin the conductivity of the sediment after centrifugalization is found to be increased, even when the conductivity of the suspending liquid is not increased or is diminished. And according to Woelfel's observations⁵⁴ when formol corpuscles suspended in cane sugar solution are acted upon by saponin, no increase in the ash of the sus-

⁵³ Journ. of Physiology, vol. xxvi, p. 480, 1891.

⁵⁴ Bio-chem. Journ., iii, p. 146, 1908.

pending liquid takes place. So we may assume that neither (b) nor (c) occurs; or that if (b) occurs, (c) does not. I have shown that saponin exerts its normal action on unfixed corpuscles in cane sugar solution.

Even in saturated cane sugar solution lacking of unfixed corpuscles is produced by saponin as rapidly as normal. It is interesting to observe how suddenly the greatly crenated corpuscles swell up and assume a spherical form before the blood pigment escapes. There is every reason to believe that saponin exerts its normal action in the presence of cane sugar on formaldehyde corpuscles too. We are left, then, to the conclusion that saponin increases the conductivity of the formaldehyde corpuscles by increasing their permeability to the ions of the serum. We have already recognized an increase of permeability of the fresh corpuscles at 0° C. as the first stage in the action of saponin and have shown that this coincides with the taking up of saponin by the corpuscles.

When cholesterin and lecithin are extracted from formaldehyde corpuscles by ether, the conductivity of the corpuscles is markedly increased and now saponin produces no effect. The inference seems clear that the saponin affects the formaldehyde corpuscles by acting on the ether-soluble substances. This action, as has been said, must be of such a nature as to permit the ions of the suspending liquid to pass more easily through the corpuscles than before. It must, therefore, certainly affect the surface layer of the corpuscles whether it exerts any action in the interior or not. This agrees very well with the idea that lipid substances form essential constituents of the surface layer of the corpuscles.

A further fact which indicates that the saponin acts on the surface layer of the formaldehyde-fixed corpuscles when it increases their conductivity is that, after the action of saponin, the corpuscles do not clump so readily as before and are more easily dispersed by shaking.

Recent work has confirmed the idea expressed by Peskind⁵⁵ that the envelope of the corpuscles is not to be considered as composed exclusively of lipoids, according to Overton's assumption,⁵⁶ but that protein, probably nucleo-protein, is also an important constituent.

⁵⁵ Amer. Journ. of Physiol. viii, p. 404, 1903.

⁵⁶ Studien Ueber die Narkose, Jena, 1901.

Höber⁵⁷ has brought forward evidence that neutral salts may alter the permeability of the superficial layer of the corpuscles by causing changes in the colloids of that layer. The series in which the ions can be arranged as regards intensity of action, under given conditions, correspond approximately to the series for precipitation of proteins (egg-albumin). But according to Porges and Neubauer,⁵⁸ who repeated the work of W. Koch,⁵⁹ although the order of the ions is the same as regards their effect on lecithin suspensions as the series found by Hofmeister and Pauli for albumin, the concentrations in which they act agree much better with the physiological limits in the case of lecithin. They therefore give to the lipoids the preponderant rôle in the envelope.

Since, in the formaldehyde corpuscles the hæmoglobin is certainly, and the other proteins probably, altered profoundly, while the corpuscles still remain practically impermeable to the ions of the serum, the suggestion is that the surface layer consists in preponderating amount of substances not essentially altered by formaldehyde.

Bile-salts. These substances can still be acted on by *bile-salts*. For sodium taurocholate causes an increase in the conductivity of formaldehyde corpuscles similar to that caused by saponin, and without any increase in the conductivity of the suspending liquid⁶⁰.

In the experiment cited, the conductivity of the control of the formaldehyde blood was 52.38, that of the formaldehyde blood after the action of the bile salt 74.78. The conductivity of the unfixed blood after laking by the taurocholate was 54.99, that of the control 59.37.

It is a point worthy of note that when unfixed corpuscles, either in natural suspension in serum or suspended in salt solution, are laked by sodium taurocholate no increase in the conductivity occurs, or rather a diminution due to the influence of liberated hæmoglobin.

Thus in one experiment⁶¹ the conductivity, at 0° C., of defibrinated blood when 28 per cent of the hæmoglobin had been liberated was 32.21. That of the control (to which sodium chloride solution had been

⁵⁷ Bio-chem. Zeit., xi, p. 35; xiv, p. 209, 1908.

⁵⁸ Bio-chem. Zeit., vii, p. 152, 1907.

⁵⁹ Zeit. für Physiol.-Chem., xxxvii, p. 181, 1903.

⁶⁰ Journ. of Med. Research, loc. cit., experiment 2.

⁶¹ Experiment 9, Amer. Journ. of Physiol., ix, loc. cit.

added so as to make up approximately for the direct increase of the conductivity of the blood caused by the addition of the sodium taurocholate solution) was 38.06. The amount of serum in the defibrinated blood was 58 per cent (by the electrical method). Taking the total hæmoglobin of the blood as 13 per cent this would give an amount of hæmoglobin in solution in the serum equal to 6.4 gr. per hundred cc. of serum. This of itself would reduce the conductivity by 11.5 per cent. Deducting this from the conductivity of the control, we get 33.7. So that at this time no sensible amount of intracorpuseular electrolytes would seem to be taking part in the conduction. After complete laking the conductivity was 33.22. If we suppose the hæmoglobin now to be uniformly distributed over the laked blood, the conductivity of the control, after making the requisite deduction for the depressing effect of the hæmoglobin in the laked blood, would be 29.1. This is certainly too low since the whole of the hæmoglobin in laked dog's blood cannot be held in solution. So that even now if intra-corpuseular electrolytes have been liberated the amount must be comparatively small. The effect on the ghosts is obviously quite different from that of saponin or water.

The explanation probably is that the bile-salt in general causes laking without entrance of water into the corpuscle, at least in moderate doses. The hæmoglobin is therefore separated from the stroma and discharged through the envelope without dissociation of stroma electrolytes to any great degree.

Bile-salt in a certain concentration seems to dissolve the envelope so rapidly that swelling of the corpuscle cannot take place, no difference of osmotic pressure being established when the envelope has been extensively injured, or when the bile-salt destroys or lessens the affinity of the corpuscle for water. It is quite in harmony with this view that when laking by taurocholate is caused to proceed very slowly some of the erythrocytes may be seen to swell up before the hæmoglobin escapes. In this connection the fact that under the influence of taurocholate, the leucocytes in *Necturus* blood swell little if at all, although they may become dim, is of interest. In water they swell greatly, as do the nuclei, the contours of cell and nucleus becoming very sharp. Here again, it is difficult to avoid the conclusion that the preservation of a relatively intact envelope is an essential condition for the entrance of a large amount of water.

Permeability of corpuscles for ammonium chloride. I endeavored to obtain evidence as to the possible condition of electrolytes in the interior of the corpuscles by investigating the absorption of ammonium chloride by unfixed and formol-fixed corpuscles. When ammonium chloride in substance is added to blood the corpuscles are not laked, although they take up the ammonium chloride freely. Notwithstanding the entrance of a relatively large quantity of ammonium chloride into the corpuscles and the presence of abundance of the ions of that salt in the serum, the corpuscles remain bad conductors like those of the original blood. Either, then, the ammonium chloride in the interior of the corpuscles is in such a condition that it does not ionize and is bound as rapidly as it enters, or the corpuscles after the affinities of the stroma have been satisfied and equilibrium has been established no longer admit any appreciable amount of ammonium chloride or, of course, of the normal serum electrolytes, although what has already entered or a portion of it may be ionized. When water is added to a sediment of corpuscles artificially enriched with ammonium chloride, electrolytes pass out of the corpuscles just as they do in the case of a sediment of normal blood, but to a much larger extent. The parallelism of the two curves shows that the ammonium chloride is escaping from the corpuscles in the same way as the normal electrolytes of the corpuscles do. We infer from this that the condition of the ammonium chloride in the interior of the corpuscles is not very different from that of the normal intracorpuseular electrolytes. Here, then, we have an instance of an electrolyte which readily penetrates the corpuscles, but whose ions, when equilibrium has been established, practically do not conduct the current from the serum across the corpuscles. The addition of water increases the conductivity of a suspension of corpuscles artificially enriched by ammonium chloride to a much greater degree than the conductivity of a suspension equally rich in normal corpuscles. This additional increase of conductivity may be due to two things; first, the liberation of ammonium chloride from the corpuscles and its solution in the serum; second, the conduction of electricity by ammonium chloride ions passing into the corpuscles from the serum when the envelopes or the corpuscles as a whole have been altered by the water. There is no question as to the first factor. That the second may have some influence is indicated by experiments

where the conductivity of the sediment of a mixture of formaldehyde-fixed corpuscles with ammonium chloride was found to be higher than that of the corresponding mixture of formol corpuscles with sodium chloride, while the conductivities of the serum of the ammonium chloride mixture and of the mixture itself were distinctly less than the corresponding conductivities for the sodium chloride mixture.

Mechanical laking. The results obtained on corpuscles laked by mechanical means (trituration with sand) are of special interest. One would suppose that this would be the most likely of all methods to permit the escape of the (hypothetical) electrolyte-colloid compounds without change. Fresh ox or sheep's blood was rubbed up in a mortar with silver sand previously incinerated and then washed thoroughly with distilled water and dried. Evaporation was prevented by covering the mortar with the copper rings of a water bath and conducting the trituration in a cool room. The rubbing was continued until the laking was practically complete, as controlled by microscopic examination and by centrifuging a small sample from time to time. Serum was separated from the defibrinated blood and hæmoglobin-containing liquid from the laked blood, evaporation being prevented by covering the centrifuge tubes with rubber caps. Freezing point and conductivity measurements were made on the original blood, on the laked blood after decantation from the sand without centrifugalization, on the serum and on the hæmoglobin-containing liquid after centrifugalization. In the experiment the results of which are quoted in Table I ox blood was triturated for twenty-five minutes. Ninety-five per cent. of the hæmoglobin was found to be in solution, representing an oxygen capacity of 22 cc. per hundred cc. of blood by Haldane's hæmoglobinometer. Besides the measurements of freezing point and conductivity a series of observations was made on the influence of dilution with water and of saponin on the defibrinated blood, the laked blood and the serum with the object of determining whether the laked blood follows the curve of a suspension of corpuscles like the defibrinated blood or of a homogeneous solution like the serum. As is seen from Table II and Fig. I, the curve for the diluted laked blood resembles that of the defibrinated blood much more than that of the serum. The same is true for the effect of saponin, which causes a marked increase in the conductivity of the laked blood and to exactly the same point as in

TABLE I.

	λ	$\lambda(5^\circ) \times 10^9$
Defib. ox-blood.....	.530 } .531 } .531 }	39.06 } 39.18 }
Serum from the defib. blood.....	.531 } .531 } .532 } .533 }	39.73* 80.22
Laked blood.....	.518 } .518 } .516 }	39.86 42.04† 42.11†
Laked blood (top).....		43.78‡ 43.93§

* After standing all night in ice-chest.

† After complete sedimentation of the sand. All night in ice-chest.

‡ After centrifuging one-half hour.

§ After centrifuging another hour.

TABLE II.

	DEFIB. OX- BLOOD.	LAKED BLOOD.*	SERUM.
	39.67	43.19	77.76
+ 1 vol. water.....	24.28	30.69	45.11
+ 3 vols. water.....	17.48	18.99	24.14
+ 5 vols. water.....	10.42	10.76	13.06
+ saponin †.....	54.52	54.52	73.48

* After separation of all the unlaked corpuscles, which made up not more than 0.3 cc. in 15 cc. of the laked blood. The blood was laked in the same way as in the experiment of Table I.

† One-tenth of its volume of an aqueous solution of saponin was added to the blood, etc. The saponin solution had a conductivity only slightly greater than that of the distilled water.

the defibrinated blood, while in the case of serum there is a small diminution of conductivity. The explanation is afforded by the microscopic observation that the laked blood was crowded with ghosts. The action of water and of saponin is obviously, in the main at any rate,

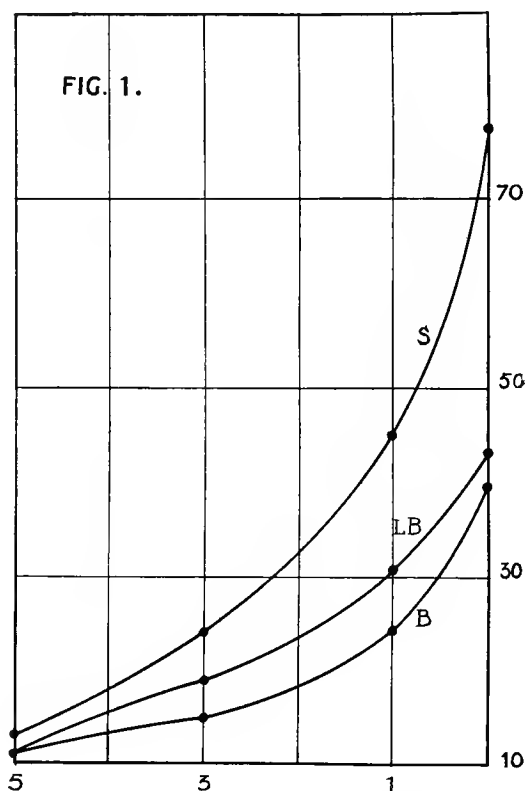


FIG. 1. Conductivities plotted along vertical and dilutions along horizontal axis. *S*, serum; *LB*, blood laked by trituration with sand; *B*, defibrinated blood.

an action on the ghosts and not on electrolyte-protein compounds liberated by trituration from the corpuscles.

In Table III, the results of an experiment in which sheep's blood was partially laked by shaking with clean mercury, according to the

method of Meltzer and Welch,⁶² are shown. It will be observed that in both methods of laking the λ of the defibrinated blood is somewhat diminished by mechanical laking. This agrees with the observation of Hamburger⁶³ and Foa⁶⁴ on the freezing-point of blood laked by freez-

TABLE III.

	λ	$\lambda (5^\circ) \times 10^8$
Serum from defib. sheep's blood.590 .593	89.90
The blood partially laked by shaking with mercury (top)582 .578 .586 .584	70.22
After further centrifuging (top)		76.13
		74.78
The laked blood*		48.19
Another specimen of the laked blood.		50.10
		51.21
The laked blood + saponin (in substance)†		69.64
The defib. blood.598 .590 .593 .588	48.38

* Forty-two per cent of the blood pigment was in solution, representing an oxygen capacity of 7.8 cc. per 100 cc. of blood, as determined by Haldane's hæmoglobinometer.

† The saponin causes only a very slight change in the conductivity of distilled water.

ing and thawing, and is in accordance with the conclusion of Moore and Roaf⁶⁵ that the osmotic pressure of the contents of the erythrocytes is normally somewhat less than that of the plasma.

⁶² Journ. of Physiology, v, p. 255, 1884.

⁶³ Archiv für Anat. u. Physiologie, p. 486, 1897.

⁶⁴ Archivio di Fisiologia, i, pp. 199, 342.

⁶⁵ Bio-chem. Journ., iii, p. 55, 1907.

Osmotic pressure of erythrocytes and of plasma. The conception of Moore and Roaf, that while there is equilibrium of osmotic pressure between the corpuscles and the plasma there is not equality, is not open to any *a priori* objection. Yet the method of proving this by direct freezing-point determinations on sediments rich in corpuscles is beset with difficulties. Höber⁶⁶ has well stated the objections to such measurements, not only in the case of blood corpuscles but also in the case of solid tissues. Doubtless, it is these difficulties which account for the fact that "in the whole extensive literature of cryoscopic measurements on blood" Moore and Roaf "have only been able to find one instance in which the freezing point of the separated corpuscles has been taken alongside that of the serum." It is obviously impossible to have that uniform distribution of fine ice-crystals in a mass like a blood-corpuscle sediment which is attainable in a liquid like serum. At best, we can stir up more or less completely frozen corpuscles. Further, we are not determining the freezing point of a homogeneous solution. Between the corpuscles are thin layers of serum in capillary spaces, in the interior of the corpuscles perhaps pockets of intracellular liquid in the interstices of the stroma, and I know of no means of assuring one's self whether or not the intracorpuseular and extracorpuseular liquids freeze at the same time, or of determining how much each contributes to the final result. The fact that the Δ of defibrinated blood is the same as that of its serum indicates that in a suspension containing abundance of serum the serum freezes at any rate as soon as the corpuscles. But in a sediment of corpuscles it might not be the same. If, now, while the real osmotic concentration were the same in the corpuscles and serum, and the intracorpuseular contents were to freeze before the serum because the latter is in much smaller capillary spaces, the first formation of ice in the corpuscles would cause an increase in their osmotic pressure by withdrawing water. Water might, therefore, pass into the corpuscles from the serum and so reduce the intracorpuseular concentration as to give too small a Δ for the corpuscles.

The influence of suspended particles on the freezing point of solutions, which has been studied by Tezner and Roska⁶⁷ may also play

⁶⁶ *Physikalische Chemie der Zelle u. Gewebe* p. 41.

⁶⁷ *Zeit. für Physiol. Chem.*, lvi, p. 495, 1908; and Tezner, *ibid.*, liv, p. 95. 1907.

a part. They showed that by adsorption dissolved substances accumulate at the surface of the suspended particles, leading to impoverishment of the suspending liquid and diminution of its Δ as compared with the Δ of the pure solution. In sediments rich in corpuscles the molecular concentration of the liquid between the corpuscles might thus be diminished, and in freezing point observations on the sediment the observed Δ might be smaller than that of the pure suspending liquid, although freezing of the intracorpuseular contents might not have occurred at all.

Cause of the low conductivity of the erythrocytes. To return to our original question as to the cause of the low conductivity of the corpuscles, the following statements are now permitted:

1. It must in part be due to a low degree of permeability for the ions of the plasma because the conductivity of the defibrinated blood is so much less than the conductivity of a dilution of the serum of the blood with a quantity of water equal in volume to the corpuscles, even when we allow for the relative increase of conductivity of the serum produced by dilution. We must assume that the corpuscles neither furnish ions to aid in the conduction nor permit the serum ions to pass as easily through them as through water.

2. It may be due entirely to the relatively low permeability of the corpuscles for the serum ions and intracorpuseular ions. Obviously, no matter how numerous the ions in the interior of the corpuscles might be, the corpuscles would still be non-conductors if the ions could not pass through them. A vesicle of fat enclosing a solution of electrolytes would conduct as badly as if the globule consisted entirely of fat.

H. Koeppe's⁶⁸ idea that we can assume with certainty that in the blood corpuscles all the salts are present in the form of neutral molecules and none dissociated since the corpuscles do not conduct, is erroneous, as I have pointed out already.⁶⁹

3. The low conductivity of the corpuscles may be due in part to the existence in them of electrolytes in the form of compounds with proteins or other colloids or in the form of adsorptates which render them for the time non-dissociable.

⁶⁸ Archiv für Anat. u. Physiologie, p. 504, 1899.

⁶⁹ American Year-book of Medicine, p. 501, 1900.

The envelope of the erythrocytes. In discussing the results of experiments with saponin on formaldehyde-fixed corpuscles several circumstances were indicated which point to this being an action on the surface of the corpuscles rather than on their interior, an action which permits ions to pass more easily through them so that a great part of the resistance which they normally interpose to the conduction of the current is abolished. The most probable analogy to this is the withdrawal or the modification of a membrane which interposes a resistance to the passage of ions in an electrolytic circuit.

This leads naturally to the question of the *existence of an envelope* in the erythrocytes. There has been much discussion as to this, especially in the case of mammalian corpuscles.

Waldeyer⁷⁰ sums up his position in these words: "Of the existence of a rigid (feste) cortical layer of the red corpuscles I am completely convinced from my own observation. But the differentiation has not yet progressed to the stage of a true membrane capable of isolation." von Ebner⁷¹ says: "One must assume that the stroma has a denser surface layer, which is insoluble in water and capable of osmotic phenomena similar to the ektoplasma of a naked living protoplast. Such a structure, which, according to Schulze, is described as a crusta, cannot be called a membrane."

Deetjen⁷² concluded that an outer envelope of extreme delicacy exists in mammalian corpuscles and claims to have demonstrated it histologically.

In a paper already cited⁷³ I described the appearances of the ghosts of mammalian corpuscles laked in various ways, especially after partial fixation, and stained. The appearances indicated the existence of a stroma, in Rollett's sense, bounded by a structure which in ruptured ghosts appeared like a ring with a double contour.

Peskind,⁷⁴ studying corpuscles in which the formation of bubbles of nitrogen had been caused by hydroxylamine hydrochlorate, showed the presence of an envelope, apparently free from blood pigment, which prevented the bubbles from escaping.

⁷⁰ Deutsch. med. Woch. Jahrg. xxi, p. 703, 1895.

⁷¹ Kölliker's Handbuch der Gewebelehre, iii, p. 741, 1902.

⁷² Archiv für path. Anat. u. Physiol., clxv, p. 283, 1901.

⁷³ Journ. of Physiology, xxvi, p. 494, 1901.

⁷⁴ Amer. Journ. of Physiology, viii, loc. cit.

Koepppe,⁷⁵ staining the shadows with methyl violet, also convinced himself that envelopes exist in mammalian corpuscles.

Löhner⁷⁶ thinks there is an ectoplasmic layer, though not a separable membrane, in the mammalian corpuscles.

In the case of amphibian corpuscles there is good evidence of the existence of a distinctly differentiated envelope. W. Preyer⁷⁷ observed, in frogs and salamanders, erythrocytes in the process of division whose membrane was visible as a fine line with double contour stretching between the two portions of the corpuscle. F. Meves,⁷⁸ however, denies the existence of a membrane in amphibian corpuscles.

In the large colored corpuscles of *Necturus* I have demonstrated the existence of an envelope which can be histologically differentiated. It stains with Löffler's methylene blue after fixation of the corpuscles. When the corpuscles are ruptured in various ways the envelope may be separated from them as a histologically distinct structure. When intraglobular crystallization is caused in these corpuscles this structure is seen to be apparently hæmoglobin-free. This is of interest in connection with the fact already mentioned, that formaldehyde, which exerts a marked action on the blood-pigment, leaves certain of the normal properties of the envelope relatively unchanged. It may sometimes be seen that under the influence of sodium taurocholate, the envelope, after becoming distinct in consequence of the formation of hæmoglobin crystals inside the corpuscles, may disappear as if eaten away or dissolved. I have elsewhere⁷⁹ developed in detail the evidence for the existence of an envelope in the *Necturus* corpuscles. I will only add here, as further corroboration, the fact that the nuclear membrane is so distinct in these corpuscles and acts in such a way under the influence of reagents that it is not possible to doubt its existence as a histologically differentiated envelope. Now, the same staining procedure which brings out the nuclear membrane brings out the envelope of the corpuscle. Swelling and shrinking of the nucleus are not necessarily produced by the

⁷⁵ Pfüger's *Archiv*, cvii, p. 86, 1905.

⁷⁶ *Archiv für mikros. Anat.*, lxxi, p. 129, 1907.

⁷⁷ *Archiv für path. Anat. und Physiol.*, xxx, 1864.

⁷⁸ *Anat. Anzeig.*, xxvi, p. 529, 1905.

⁷⁹ *Amer. Journ. of Physiology*, viii, loc. cit.

same reagents as cause swelling and shrinking of the corpuscle. It is quite easy to cause the corpuscle to swell while the nucleus remains unchanged in size, as by the action of sapotoxin, and, contrariwise, to cause swelling of the nucleus without alteration in volume or shape of the corpuscle, as by the action of sodium taurocholate. If the entrance of water into the nuclei or its exit is affected at all by the properties of the nuclear membrane, as it certainly must be, it is difficult to resist the conclusion that the passage of water into and out of the corpuscle is also influenced by the corpuscular envelope. And, indeed, it could be observed that after treatment of sublimate-fixed corpuscles with ammonium sulphide, the addition of Löffler's methylene blue caused the swollen corpuscles and nuclei to shrink to their normal size (osmotic action of the alcohol in the stain). This shrinking does not take place if the corpuscular envelope has been ruptured or so altered that it is no longer brought out by the methylene blue, even though the rest of the corpuscle appears normal. The inference is that the shrinking depends upon a property of the envelope rather than on a property of the interior stroma. For alcohol causes the passage of water out of corpuscles whose envelope is intact and therefore the osmotic pressure in the corpuscle rises, leading in turn to the passage of water out of the nucleus. If the envelope of the corpuscle has been ruptured no difference in osmotic pressure can exist between the interior and exterior of the corpuscle, and therefore the nucleus remains exposed to a hypotonic solution.

Another argument in favor of the view that the action of the formaldehyde on the superficial layer of the corpuscles is not so subversive of its normal properties as its action on the hæmoglobin and the constituents of the corpuscles more immediately related to the hæmoglobin is that corpuscles fully fixed by formaldehyde are capable of being agglutinated, or, at least, agglomerated, by specific sera.⁸⁰

Now, agglutination certainly involves some alteration in the surface layer of the corpuscles or in the relation of that layer to the agglutinating serum. The same suggestion is strengthened by another fact observed by me,⁸¹ that corpuscles fully fixed by formaldehyde cause,

⁸⁰ Cf. Noguchi: *Med. Bull. Univ. of Pennsylvania* xv, p. 327, 1902; Stewart: *Amer. Journ. of Physiol.* xi, p. 250, 1904.

⁸¹ *Amer. Journ. of Physiol.* xi, p. 250, 1904; xii, p. 363, 1904.

on injection into animals, the production of specific agglutinins and to a smaller extent of specific hæmolysins.

Now, whether the substances in the corpuscle which take up or fix specific agglutinin or specific hæmolysin are or are not identical respectively with the corpuscular constituents (agglutininogens, hæmolysinogens) which on injection of the corpuscles into animals of a different species give rise to the production of specific agglutinin or hæmolysin, there can be no doubt that there is a close relation between them. Some writers, like Liebermann⁸² and most of Ehrlich's pupils, maintain the doctrine of strict identity. Bang and Forssman⁸³ and Forssman⁸⁴ deny this. From its solubilities the active substance appears to belong to the somewhat loosely defined group of lipoids, although, as Takaki⁸⁵ points out, this is not absolutely proved. Coca⁸⁶ working with osmic acid-fixed corpuscles, obtained some results of interest in connection with my work on formaldehyde corpuscles. He finds that the specific agglutinins of rabbit's serum are quantitatively taken up by ox corpuscles fixed with osmic acid. Strongly fixed osmic acid corpuscles are still capable of binding specific hæmolysins, although they do not give rise on injection to their production. Lightly fixed corpuscles cause a slight production of amboceptor. He concludes that the capacity of protoplasmic constituents to bind specific antibodies is not always sufficient to give them the properties of antigens. But we need not assume with Bang and Forssman the complete independence of the production of antibody from the antibody-binding substance. Foreign serum seems to increase the conductivity of formaldehyde corpuscles distinctly,⁸⁷ although only slightly in comparison with saponin. The calculated conductivity is less than the actual by a small amount corresponding, perhaps, in the case of the heated serum, to the increase of conductivity produced by increasing the relative volume of suspending liquid to corpuscles. The suspending liquid separated by the centrifuge has practically the same conductivity whether heated or un-

⁸² *Bio-chem. Zeit.*, xi, p. 405, 1908.

⁸³ *Hofmeister's Beitr.*, viii, p. 238, 1906.

⁸⁴ *Bio-chem. Zeit.*, ix, p. 330, 1908.

⁸⁵ *Hofmeister's Beitr.*, xi, p. 274, 1908.

⁸⁶ *Bio-chem. Zeit.*, xiv, p. 125, 1908.

⁸⁷ *Journ. of Med. Research*, viii, p. 306, 1902.

heated serum is added. But the excess of conductivity for the suspension with unheated serum over the calculated conductivity is distinctly greater than for the heated serum suspension. The sediment of the suspension has a higher conductivity in the case of unheated than of heated serum, indicating that the permeability of the corpuscles has been somewhat increased by the unheated serum, the same change as occurs with saponin, only less marked. This is in favor of the view that the amboceptor-fixing substance of the corpuscle is not so altered by formaldehyde that it cannot act.

There is evidence that in the case of unfixed corpuscles the amboceptor alone can produce a certain change of permeability (influence of heated serum) (p. 117). The change of permeability in the formaldehyde-fixed blood is produced only by the action of the unheated serum. Yet, agglutination of formaldehyde-fixed corpuscles is caused by heated serum. Therefore, agglutination alone is not necessarily associated with increased permeability of the corpuscles to serum ions. This is an additional argument in favor of the conclusion that the agglutination and hæmolysis produced by foreign serum are not brought about by the same substance.

The precipitation of corpuscles by dilute acids and acid salts, without laking and without affecting the laking of the corpuscles after the removal of the precipitants, which has been studied by Peskind,⁸⁸ indicates that the action is on the peripheral layer of the corpuscles and that this layer is free from hæmoglobin. Peskind says that "the hæmoglobin contained in the corpuscles is not altered in the least if only the exact amount of reagent necessary to agglutinate and precipitate the corpuscles is employed. Yet all the precipitating agents in dilute solution produce alterations in solutions of the blood pigment. If moderate excess of reagent be added, the corpuscles will still be precipitated, but the blood spectrum shows no band in the red for five or ten minutes, depending on the amount of reagent employed. The same amount of reagent added to the same amount of saponin- or water-laked blood instantly changes part of the oxyhæmoglobin, and this conversion proceeds very rapidly to completion."

The recent work of Bohr⁸⁹ and others has indicated that the hæmo-

⁸⁸ Amer. Journ. of Physiology, viii, loc. cit.

⁸⁹ See Bohr's article in Nagel's *Handbuch der Physiologie*, i, p. 54, 1905.

globin in the corpuscles does not take up oxygen according to precisely the same curve as hæmoglobin in aqueous solution. This suggests that the absorption of oxygen by the corpuscles may be divided into two stages: (1) the passage of oxygen into the corpuscle through the envelope; (2) its combination with the hæmoglobin. Hüfner⁹⁰ also has remarked that a comparison of the manner in which oxyhæmoglobin in solution and blood pigment *in situ* in the corpuscles behave in the presence of reducing agents strongly suggests that in the latter case the pigment is protected from direct contact with the reducing substance in the plasma by the envelopes of the corpuscles. It would seem probable that if any portion of the original protoplasm of the colored corpuscle should be retained approximately unaltered in order to regulate the exchanges of the corpuscle and, therefore, to govern its nutrition as well as its function, it would be the peripheral portion which is in contact with the plasma. It would probably be advantageous for this that the protoplasm should not be loaded with a secondary product like hæmoglobin.

My view, then, is, that the low conductivity of the colored corpuscles, the leucocytes, and, presumably, of other cells is due (1) to the low permeability of the superficial layer of the cell for the ions of the plasma or lymph; (2) to a combination (or adsorption) of electrolytes with the proteins or other constituents of the corpuscle after their entrance into it. No evidence has been produced that all the electrolytes in the interior of the corpuscle are in such condition as to be incapable of conducting. Good evidence has been obtained that a portion of the intracorpuseular electrolytes is more easily liberated than the rest during hæmolysis. This portion may be in solution while the rest is adsorbed or combined.

Conditions governing the permeability of the erythrocytes. As to the ultimate reason of the relative impermeability of the corpuscles for the ions of the plasma, I have forborne to speculate.

It is certainly not an absolute impermeability. As Hamburger has shown,⁹¹ it is the relative impermeability for the kations only which normally prevents the passage of salts into the corpuscles, the

⁹⁰ Archiv für Anat. u. Physiologie, p. 463, 1907.

⁹¹ Ibid., p. 492, 1902.

anions being unable to enter without a corresponding number of kations. Under the influence of carbon dioxide, anions are able to pass into and out of the corpuscles. K. Spiro and L. J. Henderson⁹² have recently shown that with the aid of various substances which constitute an "inactive alkali reserve," the well-known phenomenon of the increase in the titratable alkalinity of the blood plasma under the influence of carbon dioxide can be imitated in artificial heterogeneous systems. The simplest assumption which will harmonize with the fact of the very low conductivity of the corpuscles is that the ions of the plasma and also the ions of the corpuscles, if such exist, are unable to pass except with difficulty through the bounding surface of the corpuscles. This assumption does not involve any theory of the property of the surface on which this relative impermeability depends. It can be made equally whether the impermeability is due to (a) difficulty of diffusion of the ions into or out of the corpuscle at its surface; (b) difficulty of solution of the ions in the substance of the corpuscle at its surface; (c) the relatively small adsorption of the electrolytes on the surface of the corpuscle. (d) If we do not include under adsorption, as is done by some writers, loose chemical combinations of ions with proteins or other constituents of the corpuscle, the relative impermeability may be due to the slight affinity of the outer portion of the corpuscle for these.

Any one of the possibilities mentioned may be true whether the corpuscle is homogeneous throughout or whether its outer portion is physiologically differentiated into a "Plasmahaut" or envelope, or histologically differentiated as well into an actual membrane. The existence, or the demonstrable existence, of such an envelope or of such a membrane is a question for separate consideration. The question whether, as a matter of fact, the corpuscles are relatively impermeable to certain substances, relatively permeable to others, can be investigated as such without reference to the question of the existence of an envelope.

That the serum ions in general do not easily penetrate the corpuscles may be regarded as proved, not only as a deduction from the low conductivity of the corpuscles suspended in serum, but by direct experi-

⁹² Bio-chem. Zeit., xv, p. 114, 1908.

ments.⁹³ I have myself shown, as was done later by Oker Blom, that the conductivity of isotonic sodium chloride solutions in contact with blood corpuscles remains practically unaltered. Therefore the ions of sodium chloride, quantitatively the most important ions of serum, do not easily penetrate the corpuscles even when their concentration in the serum is markedly increased. Whether this is due to low adsorptive power of the corpuscles to these ions, as Moore and Roaf suggest, really does not bear on our present question. The existence of potassium in the corpuscles, although they are also practically non-conductors when suspended in solutions of potassium salts, could only seem to be a difficulty, (a) if a special meaning were given to the term permeability, connecting it strictly with physical diffusion, for example; (b) if the impermeability were supposed to be absolute, which is not necessary to explain the low conductivity of the corpuscles; (c) if the permeability were supposed to be always the same for the undissociated molecules of a salt and for its ions; (d) if the corpuscle were assumed to preserve exactly the same degree of permeability to one and the same substance not only throughout its whole life history, with uniform external conditions, but also in different physiological states of the organs through which the blood passes or of the plasma in which the corpuscles float, and in the presence of varying concentrations of the substance in the plasma. There is no need to assume that the permeability of the developing erythrocytes is the same quantitatively and qualitatively as that of the adult cell. Nor is it our conception that the permeability is necessarily the same from hour to hour in the case of the fully formed corpuscles.

I have never asserted that either the selective permeability of the corpuscles for various substances or their reaction to various hæmolytic agents depends entirely on the properties of the surface layer. On the contrary, I have insisted on the part played by the stroma as a whole and have pointed out that the conception of the corpuscle as a vesicle, a little bladder filled with hæmoglobin solution, will not fit in with the facts of hæmolysis. I have not suggested, and do not imagine, that the permeability of the corpuscles, either for salts or for colloids, depends merely on diffusion through physical pores.

⁹³ Hedin, Eykman, etc.

Neither Traube's "atom-sieve" nor Ostwald's "ion-sieve"⁹⁴ is a very satisfying conception in the case of an animal cell, although the results of Voigtländer,⁹⁵ recently confirmed by K. Meyer,⁹⁶ show that in gelatin-gels the velocity of diffusion of salts diminishes as the concentration of the gels increases. In membranes poor in water like the shell membrane of the egg, the envelope of fat cells, the sarcolemma of muscle fibers, the neurilemma and medullary sheath of nerves, and in all probability (considering the low water content of the erythrocyte as a whole), the envelope of the colored blood corpuscles, the difficulty of diffusion of the ions may be itself a very important factor in the low conductivity.

It is not possible directly to test the question on ordinary cells whether inside the cells all the electrolytes are so bound that they do not conduct the current. In a large cell like a hen's egg, however, the question can be tested. Even if we hesitate to apply the results obtained on the albuminous coating, which conducts practically as well as an aqueous solution of the salts (apart from the ordinary depressing influence of the proteins on the conductivity) there can be no fundamental objection, so far as I can see, to applying the results obtained with the egg-yolk to the question whether ordinary cell contents conduct at all. Now, I have shown⁹⁷ that while the conductivity of the yolk is three times less than that of egg-white, it is still about one-fifth the conductivity of hen's blood serum. Whether this relatively low conductivity is due to a low degree of ionization of the salts or to mechanical causes (insulation by the fatty materials) I have not been able to show. The fact that dilution with water causes a much smaller proportional diminution in the conductivity of the yolk than in the conductivity of the egg-white might be explained as due either to the production of greater dissociation of electrolytes in the former or to mechanical separation of the fatty globules increasing the average width of the conducting paths. The want of effect of saponin on the conductivity of egg-yolk suggests again that in the ordinary cell it does not increase the conductivity

⁹⁴ Zeit. für. physik. Chem., vi, p. 71, 1890.

⁹⁵ Ibid., iii, p. 316, 1889.

⁹⁶ Hofmeister's Beitr., vii, p. 393, 1906.

⁹⁷ Journ. of Exper. Med., vol. vi, p. 257, 1902.

so much by diminishing the adsorption or chemical combination of electrolytes throughout the substance of the corpuscle as by favoring their passage through the envelope.

Membranes and Electromotive Phenomena.—As pointed out in my first paper, it is difficult to explain such phenomena as the vastly greater conductivity of nerve fibers in the longitudinal than in the transverse direction⁹⁸ except on the assumption that the membranes or envelopes, which cut the current lines in the latter case, interpose a great resistance to the passage of the ions. An adsorption or chemical combination of electrolytes in the interior of the fiber would act equally in diminishing the conductivity in whatever direction the current is allowed to flow. I do not think that anybody supposes that when nerve or muscle is stimulated electrically the current is conducted entirely by ions outside the fibers and not at all by the fiber contents. On the contrary, the most natural explanation of the inferior stimulating power of a transversely directed current is the smaller intensity of the current which traverses the contents of the fibers.

Guiffré,⁹⁹ under Hermann's direction, still obtained a marked difference in muscle even when he made the current density uniform by arranging two parallel-fibred muscles in series so that the current passed in the longitudinal direction through one and in the transverse direction through the other. He considered that he had in this way eliminated the difference of resistance as a factor in the difference between the longitudinal and transverse excitability. This, however, is not the case. For in transverse conduction much more of the current will traverse the interstitial tissue and much less the fiber contents than in longitudinal conduction, even though the average current density may be the same.

It is generally assumed that in the interior of the fibers free ions exist. They certainly exist in the vacuole contents of the cells which possess vacuoles. They exist, as already pointed out, in the contents of ova, where they are large enough to allow the question to be directly tested. They exist in the liquids expressed from all the tissues investi-

⁹⁸ Hermann, Pflüger's Archiv, v, p. 223, 1871; xxxix, p. 490, 1886.

⁹⁹ Pflüger's Archiv, xxi, p. 470, 1880.

gated and in the extracorporeal liquid of colored corpuscles laked after washing away all the serum constituents with solutions of non-electrolytes like sugar. In short, the assumption that all the electrolytes in the colored corpuscles are so bound that they cannot conduct the current is opposed to all the direct evidence and is inferred simply from the fact that the corpuscles have a low conductivity, a phenomenon more simply explained by assuming that the envelopes which are known to exist in the case of certain kinds of colored corpuscles, at least, are not freely penetrated by ions. Nearly a dozen years¹⁰⁰ ago I pointed out the far-reaching relations of the low electrical conductivity of cells, whether due to badly conducting envelopes or not, in the explanation of many of the electrical phenomena of muscle and nerve, electrotonic currents and other so-called polarization phenomena, the high degree of polarizability of these tissues as compared with the polarizability of the surface of contact of ordinary solutions of electrolytes, etc.

In later papers¹⁰¹ it was pointed out "that the decided increase which I found in the potential difference between the belly and tendinous extremity of the frog's gastrocnemius, when sapotoxin solution (in salt solution) is applied to the muscle next the tendon, may be due either to a change in the permeability of the sarcolemma or to liberation of electrolytes in the fiber contents or to both. A similar though less marked increase is produced by sapotoxin in the current of rest of nerve." Also¹⁰² that the increase of conductivity which is known to occur in dying muscle may be due not only to increased formation of ions in the muscular substance, but to a change in the permeability of the muscular membranes. Numerous writers have since applied similar ideas to the detailed discussion of the electromotive properties of the tissues, including Macdonald, in a series of important papers¹⁰³ Bernstein;¹⁰⁴ Brünings;¹⁰⁵ Cremer;¹⁰⁶ Tschagonetz,¹⁰⁷ who refers to an

¹⁰⁰ Journ. Bost. Soc. Med. Sc.; Centralb. f. Physiol., loc. cit., 1897.

¹⁰¹ Amer. Journ. of Physiol., ix, p. 75, 1903.

¹⁰² Journ. of Exp. Med., vi, p. 259, 1902.

¹⁰³ Thompson-Yates Laboratory. Rep., p. 213, 1902, etc.

¹⁰⁴ Pflüger's Archiv, xcii, p. 521, 1902.

¹⁰⁵ Ibid., xcviii, p. 241; Ibid., C, p. 367, 1903.

¹⁰⁶ Zeit. für Biol., xlvii, p. 562, 1906.

¹⁰⁷ Ibid., I, p. 247, 1907.

earlier paper of his published in Russian in 1896. Quite recently R. S. Lillie¹⁰⁸ has made a valuable contribution on the relation of the "membranes" of contractile tissues to their electromotive phenomena.

The objection of Moore and Roaf¹⁰⁹ to the existence of a "membrane" which takes part in the regulation of the exchanges between the blood corpuscles and the plasma and especially in the regulation of the exchange of electrolytes is based, it seems to me, upon a special conception of the properties of the membrane. There is no *a priori* reason for denying to the envelope any of the powers of the protoplasm. When we have determined that a given substance passes easily, another with difficulty, into a corpuscle whose peripheral layer is histologically differentiated from its interior, we know no more about the mode of passage of the first substance, the cause of the hindrance of the passage to the second, than if the histological envelope had not been demonstrated. We have to inquire in the one case as in the other whether there is anything in the relative solubility of the two substances in the surface layer of the cell or in any of its constituents; whether there is any difference in the adsorptive power of that layer for the substances, or such a difference in its chemical affinity for them as will give the clue to the difference in the permeability of the cell to the two substances. We cannot say that it is "very unlikely that a membrane would allow hæmoglobin to pass out of the corpuscles while keeping back the electrolytes" unless the nature of the membrane in question is specified. Kahlenberg¹¹⁰ has indeed shown that the current view that crystalloids always pass through membranes more readily than colloids is untenable. Just the opposite may occur. It depends, as Tamann,¹¹¹ l'Hermite¹¹² and others showed long ago, upon the affinity of the substances for, or their solubility in the membrane.

Moore and Roaf¹¹³ made some interesting experiments on the passage of electrolytes from erythrocytes and from serum through dialyser membranes after treatment in various ways. They consider that these experiments afford evidence that the electrolytes in the corpuscles are

¹⁰⁸ Amer. Journ. of Physiol., xxii, p. 75, 1908.

¹⁰⁹ Bio-chem. Journ., iii, p. 55, 1907.

¹¹⁰ Journ. of Physical Chemistry, x, p. 141; Trans. Wisconsin Acad., Mar., 1906; Chem. Zentralblatt, i, p. 1391, 1906.

¹¹¹ Zeit. für. physikal. Chem., x, p. 255, 1892.

¹¹² Comp. rend., xxxix, p. 1177, 1854.

¹¹³ Loc. cit.

bound or adsorbed in such a way that they do not conduct, and that such compounds or adsorbates are kept back by the dialyser even after liberation from the corpuscles. Perhaps, however, they have not taken sufficient account of the retention of salts by the ghosts.

The increase of conductivity in these experiments when the corpuscles are laked by freezing and thawing is probably due to two things: (a) escape of a portion of the electrolytes and some water from the corpuscles; (b) the consequent diminution in the total volume of the corpuscles now represented by ghosts, with possibly some increase in the permeability of the ghosts to ions. The increase of the temperature to 40° C. for the conductivity measurement after the freezing and thawing might be expected to cause the liberation of a greater amount of electrolytes than in my observations, where the conductivity was measured at a much lower temperature.

The further increase in conductivity on dialysis against distilled water is due, mainly at least, to escape of a further quantity of electrolytes from the ghosts, under the influence of dilution, not to the breaking up of combinations still existing between the electrolytes and colloids after they have been liberated.

After the addition of ether to blood in quantity sufficient to cause rapid laking no ghosts could be seen, but only masses of granular débris.¹¹⁴ After water-laking probably every corpuscle is represented by a ghost. It is therefore easy to explain why more electrolytes were found in the dialysate after ether than after water, without assuming that adsorbates are broken up by the ether after liberation from the corpuscles. In the same way, the conductivity of the blood laked by saponin is further increased by heating the laked blood to the temperature at which heat itself causes laking. The final conductivity is about the same as when the same amount of saponin is added to heat-laked blood. The slight excess of conductivity in the former case is accounted for by the survival of fewer ghosts.

The final increase in conductivity on incineration is explained, as before, by the consideration that the ghosts even after water-laking still retain a considerable portion of salts. Doubtless, these salts are in part, at any rate, bound in the ghosts. The same explanation holds for the much smaller proportion of salts and the much smaller Δ of the dialysate from the corpuscles than of the dialysate from the serum.

That the stromata after certain methods of laking still remain relatively

¹¹⁴ Stewart, *Journ. of Med. Res.*, viii, p. 283, 1902.

impermeable to certain salts, although the hæmoglobin has just passed out of them, follows from the fact that the ghosts shrink in hypertonic sodium chloride solutions as normal corpuscles do, and that the conductivity of a sediment of ghosts suspended in serum or sodium chloride solution is very small.

They occupy a far larger relative volume of the laked blood and, therefore, exercise a far greater effect on its conductivity than might be supposed from the comparatively scanty sediments which can be separated by the centrifuge. Nothing can be more inappropriate than the terms "rupture of the corpuscles," "breaking up of the corpuscles," "solution of the corpuscles," etc., often applied to the changes in hæmolysis. The laked blood is not a homogeneous solution. The main reason why its conductivity is not equal to that of a solution of the ash of the corpuscles and serum occupying the same volume is that much of the electrolytes is still in the ghosts, probably in the form of compounds of some kind. Another reason is that the ions of the serum and of the corpuscular contents already liberated cannot easily penetrate the ghosts. A certain portion of the electrolytes of the ash of course comes from lecithin and other compounds which are not electrolytes, by the oxidation of phosphorus, *e.g.*

The results of Roaf and Alderson¹¹⁵ on the dialysis against water of erythrocytes treated with chloroform, ether, acetic acid, etc., must be interpreted in view of the same considerations. In most, though not all, of their experiments, a larger amount of electrolytes dialysed out when the corpuscles had been treated in this way than when they were dialysed against water without treatment. This may be due, and very likely is due in part, to the setting free of electrolytes from combinations of some kind within the corpuscles and not to an alteration of the corpuscles which permits electrolytes already free to pass out of them. But the experiments do not prove this. For although it was seen that the corpuscles (dialysed against water) in the control experiments were completely laked, only their ghosts being left, this throws no light on the questions, how much of the electrolytes had left the ghosts and in what way the residue still within the ghosts was retained. A shadow laked by foreign serum has the same appearance under the microscope as a shadow laked by saponin. Yet the serum-laked ghost retains a much larger proportion of its electrolytes. The existence or the rôle of the envelope, if it does exist, cannot be determined in this way. The

¹¹⁵ Bio-chem. Journ., ii, p. 412, 1907.

fact, very well illustrated in these experiments, that electrolytes do leave the erythrocytes under the influence of anæsthetics may partly explain the increase in the osmotic concentration of the blood during ether and chloroform anæsthesia observed by Carlson and Luckhardt,¹¹⁶ although they consider that the main factor is the presence of the anæsthetic itself in the serum.

PART II. THE MECHANISM OF HÆMOLYSIS

Hæmochromolysis and stromatolysis. Adopting for the pigment in its natural condition within the corpuscle Bohr's term "hæmochrome," I conceive of hæmolysis as follows: We have to distinguish in this process the mere liberation of the blood pigment, or hæmochromolysis, from the more or less complete destruction or solution of the stromata, stromatolysis. Hæmochromolysis *plus* stromatolysis constitutes erythrocytolysis. Unfortunately the term hæmolysis has been applied indifferently to any process which causes liberation of the blood pigment from the corpuscles, being equivalent sometimes to hæmochromolysis, sometimes to erythrocytolysis.

Hoppe-Seyler¹¹⁷ considered the native blood-pigment in the corpuscles to be a compound of hæmoglobin with lecithin. Now in the body lecithin shows a marked tendency to unite with other substances, including proteins.¹¹⁸ So that we may perhaps conceive of the hæmochrome complex as a hæmoglobin-lecithin-protein combination, a combination which is very easily broken up so as to yield hæmoglobin. Bang¹¹⁹ has shown that lipid substances, especially bodies like lecithin, may under certain conditions be fixed by hæmoglobin, possibly in the form of adsorptates.

Sjövall,¹²⁰ in his study of the staining reactions of the nerve cells and fibers with osmic acid, has brought forward evidence that water breaks up a loose compound between the lipoids and the rest of the cell contents. And Albrecht;¹²¹ quoted by Bang,¹²² states that a similar decomposition

¹¹⁶ Amer. Journ. of Phys., xxi, p. 162,

¹¹⁷ See Bohr's article in Nagel's Handbuch der Physiologie, i, p. 90.

¹¹⁸ See Glikin in Oppenheimer's Handbuch der Bio-chemie., i, p. 128, 1908; Bang, Ergebnisse der Physiologie, Jahrg. vi, p. 136, 1907.

¹¹⁹ Loc. cit., p. 152.

¹²⁰ Anat. Hefte, 1905.

¹²¹ Verh. der Anat. Ges., 1902.

¹²² Ergebnisse der Physiol., vi, 1907.

resulting in the setting free of lecithin in the protoplasm of various cells, takes place spontaneously after death.

The essential thing in liberation of the blood pigment is the change of the hæmochrome, which exists in colloid or solid solution or perhaps as an adsorbate in the stroma or as a weak chemical combination with the stroma, into an aqueous solution of hæmoglobin, or, at any rate, into an aggregate condition which by comparison with its normal condition in the corpuscles may be denominated water-rich. Given such an aqueous solution of hæmoglobin in the interior of the corpuscle, its liberation follows inevitably. Water-soluble hæmoglobin never exists in the corpuscle till the moment of laking arrives. It is foreign to the corpuscles and is promptly extruded. The mechanism of this expulsion of the hæmoglobin is certainly an interesting subject of study and to that we shall return. But let it be repeated, on our view the essential thing is the alteration of the natural blood pigment in the interior of the corpuscle. All the fundamental phenomena of hæmochromolysis may indeed occur, as in *Necturus* corpuscles, without liberation of the hæmoglobin from the corpuscle. The hæmoglobin of these corpuscles crystallizes so readily that by proper graduation of the dose of hæmolytic agents the hæmoglobin liberated in their interior may be crystallized before it can escape. The entrance of such an amount of water from the suspending liquid as will dissolve the crystals, or perhaps the liberation of a sufficient amount of the intra-corpuscular water, leads to the instant escape of the hæmoglobin.

Löffler's methylene blue (alcohol action) causes intraglobular crystallization without swelling of the corpuscles or nuclei. Here the crystallization is not determined by increase of water in the corpuscles. What determines it? Perhaps precipitation of proteins, which allows the hæmoglobin to separate from the stroma, perhaps the solution of lipoids. Occasionally *Necturus* corpuscles become globular under the influence of Löffler's methylene blue, and these do not show intraglobular crystallization. Probably the explanation is that when the alcohol alters the envelope in such a way that much water penetrates it the hæmoglobin passes into solution and is then liberated, whereas the entrance of alcohol without upon the whole any water having gone into the corpuscles causes such a change that hæmoglobin crystals are formed. Intraglobular crystallization in partially dried

Necturus blood may be due to the entrance of water through the altered envelopes of the corpuscles. An alteration of the envelopes such as permits the escape of hæmoglobin is therefore not the primary phenomenon in hæmolysis, but rather an alteration in the nature or in the relations of the blood pigment within the corpuscle.

Escape of the hæmoglobin solution through the envelope may be due to (1) the altered molecular condition of the stretched envelope when the corpuscle is swollen by the entrance of water; (2) a chemical or physico-chemical action of the hæmoglobin or the water on the interior surface of the envelope. J. Traube¹²³ states that hæmoglobin has a hæmolytic action, and it may therefore be supposed to act on or be taken up by some constituent of the envelope. In virtue of this action the hæmoglobin passes through the envelope, coming into contact at the outer surface of the envelope with water or a saline solution, in which it readily dissolves. If it is lytic for the corpuscle it is easy to see why the existence of an aqueous solution of it in the interior of the corpuscle is incompatible with the integrity of the latter. The point to be noted is that hæmoglobin is a foreign substance to the corpuscle, and there is no evidence that it can be regenerated to hæmochrome. Its liberation may therefore be a phenomenon belonging to the same group as the excretion of hæmoglobin from the blood by the kidney when it exists in sufficient amount in solution in the plasma. Only, in the kidney the hæmoglobin affects the cells in such a way that it passes from its solution into the cells, whereas in the case of the laked corpuscle it passes from solution in the cell contents through the substance of the cell into the blood plasma. It is certain, however, that the liberation of the hæmoglobin from the corpuscles in the act of laking is not a matter of mere diffusion. For the ghosts separated from laked blood contain much less hæmoglobin than an equal volume of the suspending liquid. And ghosts once completely freed from hæmoglobin do not take it up again from the hæmoglobin-containing liquid. It might be supposed that the affinity or the adsorptive power of the stroma for hæmoglobin had been lost by the passage out of the corpuscles of the constituents by which the blood pigment is bound or adsorbed within them. Or, again, the hæmolytic power of

¹²³ Traube and Clara Goldenthal, *Bio-chem. Zeit.*, x, p. 390, 1908.

hæmoglobin might be supposed to prevent the ghosts from re-accumulating that pigment. This, however, is unlikely because the hæmolytic power of hæmoglobin, acting outside the corpuscles, is comparatively slight, so slight that hæmolysis may remain incomplete for many hours in the presence of a large amount of hæmoglobin in the solution. Further, the hæmolytic action of the blood pigment is antagonized by serum (an antagonism which, of course, would not affect hæmoglobin acting in the interior of the corpuscles), yet ghosts take up no more hæmoglobin from a serum solution of hæmoglobin than from an aqueous solution. The most probable explanation of the failure of ghosts to take up hæmoglobin is that the envelope has no affinity for this substance. In the intact corpuscle it is free from hæmoglobin for this reason, and normal corpuscles do not take up hæmoglobin from a solution of it in serum, a fact which I have made the basis of a method of estimating the relative volume of corpuscles and plasma in the blood.¹²⁴ There is nothing surprising in the fact that hæmoglobin in the process of laking should pass out of the corpuscle through the envelope, while after laking it will not pass in the reverse direction. For, firstly, the hæmoglobin in the one case is in solution in blood serum, or other suspending liquid; in the other case, in solution in the contents of the corpuscle, or in some other relation to them than that of a solution.

Irreciprocal permeability for a given substance may just as well be produced by a difference in the condition of the substance on the two sides of a homogeneous membrane as by a difference in the nature of the two surfaces of a membrane exposed to identical solutions.

In the second place, if the envelope of the cell is histologically differentiated on the side of the cell contents, it might be expected that in accordance with the law of W. Gibbs recently used by Traube in the discussion of hæmolysis, the external and internal surfaces of the membrane should exhibit physico-chemical differences leading to irreciprocal permeability even of a substance in similar solution in contact with these two surfaces. For the passage of substances from the plasma into the outer surface of the envelope and of substances from the cell contents into its inner surface would render the two surfaces eventually heterogeneous.

¹²⁴ Journ. of Physiology, xxiv, p. 356, 1899.

Thirdly, there is reason to believe that the condition of the envelope of the corpuscle does not remain the same as regards its physico-chemical properties during the whole process of laking. For example, at the time when hæmoglobin is about to pass out, in some forms of laking, it seems that the permeability of the envelope to certain ions is increased, to diminish again after the liberation of the hæmoglobin.

This is shown by the fact that after various forms of laking the swollen ghosts are caused to shrink by the same hypertonic solutions as cause shrinking of the intact corpuscles. Even when the corpuscles in the act of laking swell up in hypertonic solutions in which they were previously crenated, the very same hypertonic solutions may cause the ghosts to shrink. It is not quite the same envelope, then, through which the hæmoglobin makes its exit in laking and which it refuses to enter after the laking is finished.

The question whether it is possible for stromata from which hæmoglobin has been liberated by the gentlest means—that is, with the least possible alteration of the stromata themselves—to regenerate hæmochrome, does not enter into the discussion. If they could do so, we might expect the expulsion of the hæmoglobin to be the first step, or, rather, an essential preliminary to regeneration of the blood pigment within them. But whether they possess this power or not, they certainly did as erythroblasts possess the power of forming hæmochrome, and the getting rid of the hæmoglobin might be looked on as an attempt on the part of the protoplasm of the erythrocytes to put itself once more in the position of the colorless erythroblasts before the formation of the hæmochrome began. The absence of nuclei in the mammalian corpuscles, even if we assume the absence of diffused nuclear substance, is not a relevant objection.

As regards the structure of the erythrocyte, in its relations to hæmolysis, a brief recapitulation of our conception¹²⁵ may be permitted. The corpuscles consist of a protoplasmic groundwork bounded externally by an envelope. In large corpuscles, like the *Necturus* corpuscle, this envelope is better differentiated than in mammalian corpuscles and, therefore, more easily demonstrated histologically. The envelope and stroma consist essentially of lipoids (lecithin,

¹²⁵ Cf. Peskind, Amer. Journ. of Med. Sciences, p. 1011, 1904.

cholesterin), proteins (nucleoproteins), with of course, water and salts. The interior stroma, but not the envelope, is impregnated with blood pigment, either loosely combined or adsorbed by it. When gentle hæmolysis occurs, a change is produced in the envelope by the action of the hæmolytic agent on one or more of its constituents. This change permits the entrance of a certain amount of the hæmolytic agent as well as in general a certain amount of water. By the action of the hæmolytic agent (or the water) on the stroma, the relation of the blood pigment to it is altered so that the pigment goes into aqueous solution or becomes water-soluble. This is aided in most cases by the entrance of water into the corpuscle from the suspending liquid. The envelope allows hæmoglobin in watery solution to pass out through it. As shown by O. Pascucci¹²⁶ an aqueous solution of hæmoglobin cannot be retained by an envelope consisting of cholesterin or of lecithin and cholesterin after the action of saponin, solanin, cobra poison, etc.

The objection of Pascucci¹²⁷ that the lipid content of the corpuscles is too high to allow us to suppose that the lipoids belong to a stroma, a protoplasmic groundwork filling up the corpuscle, and that the analogy is rather with a sheath, like the medullary sheath of nerves, proves nothing. In the development of the hæmoglobin, it is to be supposed that the globin represents a great part of the original protein content of the protoplasm, the pigment portion of the molecule being everywhere distributed uniformly in combination with the globin. It results from the fact that so large a proportion of the original protein of the protoplasm is taken up in forming the globin, that the proportion of lipoids in the stromata appears high. Distributed over the whole protein of the corpuscle it is not so. Pascucci's objection to the existence of an interior stroma, that when intraglobular crystallization is induced we see only crystals and nothing between them, is not cogent. The material between them is colorless, and after the hæmoglobin has separated must certainly be rich in water. It is easy to see that when partially fixed corpuscles are laked, the interior of the corpuscle is not empty even when all the blood pigment has passed out. If the globin represents a part of the original protoplas-

¹²⁶ Hofmeister's Beitr., vi, p. 552, 1905.

¹²⁷ Ibid., p. 543, 1905.

mic protein, it is easy to see that through it the hæmoglobin molecule may be anchored to the stroma, the globin having affinities both with stroma and with hæmochromogen. When water enters the corpuscle in more than a certain amount the hæmoglobin—in virtue of its solubility in water—parts company with the stroma, the chief constituents of which are insoluble in water, and thus the hæmochrome complex is ruptured. In like manner, if a substance like saponin which is capable of dissolving lipoids but not proteins or hæmoglobin enters the corpuscle in sufficient amount, the lipoids of the stroma go into solution, thus parting company with the hæmoglobin. It may be that till the moment when separation between the hæmoglobin and the stroma arrives, the hæmoglobin molecule does not exist as such, but only as a complex containing the pigment hæmochromogen, the globin and the stroma constituents with which the globin is united.

When the complex decomposes under the influence of ordinary hæmolytic agents which do not act destructively upon the blood pigment, hæmoglobin is always formed because the affinity of the globin for the hæmochromogen is stronger than for the stromata.

Comparatively little is known about the chemistry of globin, and especially about the nature of the union between it and the pigment part of the hæmoglobin molecule on the one hand and the stroma on the other. It is a histon, and as such soluble in water, from which it is precipitated by especially small quantities of ammonia. It is then dissolved with special ease in excess of ammonia. Ammonium salts hinder its solution in not too great quantities of ammonia.¹²⁸ With acids histons form salts, which in the case of the inorganic acids are soluble in water. It is possible that these reactions are concerned in laking by alkalis and acids as well as in water laking.

Hæmochromolysis, then, may be produced in two ways: by dissociating the complex, by exposing it to water—that is, by an increase in the water content of the corpuscle—or by dissolving the stroma without necessarily increasing the water content. In the case of many laking agents the two factors act together. A typical instance of such agents is saponin, which increases the permeability of the corpuscles to ions by acting on the lipoids of the envelope, and thus per-

¹²⁸ Samuely, Oppenheimer's *Handbuch der Bio-chem.*, i, p. 306, 1908.

mits water to enter, while at the same time, if the dose is sufficient, it acts directly on the stroma-hæmoglobin combination. When just enough saponin is used to liberate all the hæmoglobin, the action may be considered as approximating to a pure water action. That is to say, the minimal dose of saponin need not cause any other change than the increased permeability of the corpuscle. Laking will follow from this alone. This is the condition in which a relatively small quantity of electrolytes leaves the corpuscles with the hæmoglobin. If more saponin be added to the ghosts a further action takes place which, under certain circumstances, breaks up the ghosts completely and under all circumstances causes a relatively large escape of electrolytes from them. With a supraminimal dose of saponin added to the corpuscles at once, the two actions go on together.

Water itself acts also in both ways, since the addition of it to stromata laked by gentle means results in the liberation of a relatively large amount of electrolytes. Whether the water passes into the corpuscles on account of difference of osmotic pressure, in the orthodox sense, or by reason of an affinity for water on the part of constituents of the envelope or stroma, it certainly acts on the envelope, as shown by the agglutination which precedes hæmolysis. It may do this either by producing imbibition of the lecithin or by acting on the nucleo-protein. A similar action on the whole stroma of the already gently laked corpuscle may take place, one sign of the decomposition being the setting free of electrolytes.

That there is something in the nature of a stroma in which the blood pigment is distributed is well illustrated by the behavior of sublimate- or formaldehyde-fixed corpuscles when caused to swell and shrink after a certain degree of fixation has been reached. The same observations show that the blood pigment need not be assumed to be in solution in the corpuscles in order to explain its uniform diffusion throughout the stroma, whether the corpuscle is caused to swell or shrink. At a time when the fixation has gone so far that none of the pigment escapes from the swollen corpuscle, the tint of the corpuscle remains perfectly uniform. There is no appearance of granulation of the pigment. Yet, on rubbing up the corpuscles thoroughly with sand no trace of pigment passes into the suspending liquid, although microscopic examination shows that the corpuscles have been triturated

into fragments. The pigment does not go into solution although brought into contact with an aqueous liquid because it has been rendered insoluble in water. Yet, when the corpuscle swells, the pigment remains equally distributed over it and it appears exceedingly pale. When the corpuscle shrinks the pigment assumes its original distribution and tint. The process reminds one of the paling and pigmentation of frog's skin when the pigment cells contract and relax. It is difficult to see how a mass of precipitated hæmoglobin or met-hæmoglobin such as we know them outside the corpuscles would continue to be quite uniformly distributed when the corpuscle is swollen and would return to its original and still uniform concentration when the corpuscle was made to shrink to its original volume. One would have expected rather, if the mass of blood pigment was simply enclosed in an envelope which in virtue of osmotic changes became first distended and then retracted, that a separation of the pigment from the envelope would take place during the distention. Nothing of the kind, however, occurs.

A certain amount of electrolytes accompanies the hæmoglobin in its passage out of the corpuscle, either electrolytes which are normally in aqueous solution in the cellular liquid or electrolytes separated from the stroma at the same moment as the hæmoglobin and going into aqueous solution along with the pigment, or, possibly, electrolytes split off later from the stroma by the dissociating influence of the water which has entered. If the action of the hæmolytic substance is just sufficient to cause liberation of all the hæmoglobin, a great part of the electrolytes of the corpuscles still remain in the stroma. The electrolytes which still remain may represent: (1) that portion which is more firmly bound to the stroma than the portion which escapes, constituting as it does the electrolytes necessary for the physiological condition of the protoplasmic groundwork; (2) a portion of the electrolytes in aqueous solution which is unable to escape either because the envelope is impermeable to them throughout the whole process of laking, or because, although permeable while the corpuscle is still swollen, it becomes impermeable again after the discharge of the hæmoglobin. Such a change in the permeability of the corpuscle is illustrated by the fact that in the process of formaldehyde-fixing the corpuscle at first becomes more permeable than normal to sodium chloride, but later on regains its original impermeability.

When the action of the laking agent is more intense, electrolytes are split off from the stroma and escape through the still more altered envelope and electrolytes already in solution in the ghosts, but unable to penetrate the envelope, now become capable of doing so. For reasons given in Part I the conclusion was drawn¹²⁹ that "the increase of permeability of corpuscles produced by saponin is probably caused by a corrosive, dissolving or emulsifying action of the saponin on some non-protein constituents of the envelope or stroma." Evidence was also obtained that "in the first stage of the action of saponin on unfixed blood there is an increase in the permeability of the corpuscles for ions even before any hæmoglobin has been liberated." It was suggested that "the liberation of the hæmoglobin may be secondary to this owing to the entrance of water consequent on the disturbance of osmotic equilibrium."¹³⁰ I showed, however,¹³¹ that although the increased permeability of the corpuscles, which entails the entrance of water, is a stage, and doubtless an important one, in many kinds of hæmolysis, it is not the whole process.

For, firstly, laking of crenated corpuscles may take place without swelling under the influence of sodium taurocholate. Secondly, laking may take place on the addition of any of the ordinary chemical hæmolytic agents, in substance, to a sediment of corpuscles with so small a quantity of serum between them that even if the whole of the water of the serum enters the corpuscles it would not be sufficient to produce ordinary water laking.

The red corpuscles are exceedingly poor in water compared with other cells, the solids constituting more than 40 per cent of the total mass, whereas in thymus leucocytes according to Lilienfeld, the solids make up only 11.5 per cent of the whole. So far as I know, the water content of erythroblasts before development of the blood pigment has not been determined. Yet we can assume that in developing the blood pigment in their interior the erythroblasts in all probability become poorer in water. It is an interesting speculation whether this has any relation to their function. There may be two reasons—one functional, the other physico-chemical: (1) to increase the oxygen-

¹²⁹ Journ. of Physiology, xxvi, loc cit., Journ. of Exp. Med., vi, p. 257, 1902.

¹³⁰ Amer. Journ. of Physiology, ix, loc cit.

¹³¹ Journ. of Med. Research, loc cit.

binding capacity of unit volume of the blood and therefore to facilitate rapid aëration in the lungs and rapid giving up of oxygen in the tissues without too great a blood velocity; (2) to permit the existence of the blood pigment as a gel. It seems probable that a body so soluble in water as hæmoglobin would pass into aqueous solution, or a body so capable of dissociation as hæmochrome in the presence of water would be dissociated so as to yield hæmoglobin, if the water-content of the erythrocytes were as high as that of the leucocytes. As a matter of fact, when an amount of water considerably less than that required to increase the water content of the erythrocytes to an equality with that of leucocytes is introduced into them, the hæmoglobin passes into aqueous solution and is discharged. In the case of *Necturus* corpuscles a still smaller quantity of water causes the transformation of the hæmochrome *in situ* into crystalline hæmoglobin, which is only liberated from the corpuscles when the further amount of water necessary to dissolve the crystals is introduced.

In the replacement of the hæmochrome gel by the hæmoglobin sol or solution, I see a decisive event in hæmolysis. Complete hæmochromolysis may, however, not be accompanied by marked stromatolysis; in part this depends on the quantity of the hæmolytic agent employed, in relation of course to the sensitiveness of the corpuscles, in part on the nature of the hæmolytic agent. Some laking agents, even in quantities more than sufficient to liberate all the hæmoglobin, do not destroy the stromata nor even set free any great amount of stroma electrolytes. Such are the biological laking agents. Others, even in amounts only sufficient to liberate all the hæmoglobin, seem to produce considerable changes in the stroma, characterized for one thing by the liberation of stroma electrolytes. Such an agent is water. Others still, like saponin, heating, freezing and thawing, produce complete liberation of the hæmoglobin, while the stroma is not much affected, if a strictly minimal action has been sought for; but marked effects are produced on the stroma when the action is allowed to become more intense.

It is perhaps the poverty of the erythrocytes in water which renders them so sensitive to the action of hæmolytic agents, since so many of these are known to cause the passage of water into the corpuscles as a preliminary to laking. Even where an artificial erythrocyte,

like a formaldehyde-fixed corpuscle, is laked by heating in ammoniacal water, or a formaldehyde corpuscle treated with ammonia and then washed till ammonia ceases to be given off is simply heated in water, marked swelling of the corpuscles (entrance of water) is necessary before laking takes place. The slight drying of the corpuscle which is necessary to determine laking in the presence of extracorporeal water in the form of solutions which do not lake normal corpuscles is another proof that the erythrocyte exists in a state of unstable equilibrium as regards water, even if the limits within which the water-content may vary are comparatively wide.

The normal range of "osmotic resistance" of the corpuscles may be not much greater than the range within which the osmotic pressure of the plasma in particular capillaries may vary even in health. In the kidney, for example, where a secretion whose molecular concentration is in general much greater than that of the plasma is formed, the molecular concentration of the plasma on the whole must sink. The diminution may be very considerable in particular renal capillaries or capillary tracts. During absorption of water from the intestine the same thing may occur. In disease it may be expected that such changes should be exaggerated, and it is possible that various forms of hæmoglobinæmia may be due to a hæmolysis thus caused or favored. On the other hand, in the salivary glands during active secretion a liquid of much lower molecular concentration than the plasma is separated and therefore here the molecular concentration of the plasma must increase. The changes in the plasma of blood drawn from a large vessel will, of course, be no index to the possible changes in special capillary tracts. It is plain, then, that the colored corpuscles must be fitted to withstand considerable variations in the osmotic pressure of the plasma. This is in addition to the changes produced by alterations in their permeability occasioned, for instance, as Hamburger has shown, by variations in the carbon dioxide content of the blood in different regions. Undue stress has been laid on the relative constancy of the average concentration of the blood plasma, a constancy which tends to obscure the continual and rapid vicissitudes of osmotic pressure experienced by the corpuscles as they pass along the vascular system. If the velocity of the blood stream is pathologically diminished in any portion of the kidney or intestines while the excretion of

solids or the absorption of water is not, or is not so much interfered with, the permissible limit of hypotony may be passed and intra-vascular hæmolysis may result. Since in water-laking agglutination precedes the liberation of the blood pigment, it is conceivable that local thromboses may be caused in this way. It is possible that the older erythrocytes may normally succumb in such regions of low osmotic pressure.

In his studies on *Bothriocephalus anemia* Tallquist¹³² obtained from the proglottides of the worm a substance of strong hæmolytic properties and the chemical characters of a lipid. This substance, according to his statements, caused in animals slight but distinct anemia with the characters of pernicious anemia. This seemed to strengthen the position of those who hold that progressive anemia is due to an enterogenous autointoxication. However, E. Bloch¹³³ failed to obtain from the feces of a person suffering from progressive anemia any substance corresponding in its action to Tallquist's lipid. Indeed, the substances extracted by ether or alcohol from the feces of a healthy person possessed the stronger hæmolytic action. It is quite possible that substances which produce these forms of anemia, if they are derived from the bowel, may exert their hæmolytic action, or a part of it, indirectly by injuring, in the first instance, the intestinal epithelial lining, rendering it more permeable than normal to water in the direction from the lumen to the blood and lymph, or more permeable than normal to dissolved substances in the direction from the blood or lymph to the lumen of the gut. In either case such areas of hypotony as have been suggested would be produced in certain vascular tracts in the intestinal wall. In paroxysmal hæmoglobinuria vasomotor changes associated with exposure to cold may conceivably give rise to such hypotonic regions, in which, of course, the hæmolytic action of the serum (plasma) studied by Donath and Landsteiner;¹³⁴ by Hoover and Stone¹³⁵ and by others, would be reinforced by the hypotony.

The action of salts and other substances, like cane sugar, which do

¹³² Zeit. für. Klin. Med., lxi, cited by Bloch.

¹³³ Bio-chem. Zeit., ix, p. 498, 1908.

¹³⁴ Münch. Med. Woch. lxi, p. 1590, 1904.

¹³⁵ Archives of Internal Medicine, Nov. 1908.

not easily penetrate the corpuscles, in inhibiting certain kinds of hæmolysis, for example, hæmolysis by foreign serum, is probably in part an osmotic action which hinders the entrance of water into the corpuscles, the water being unable to enter from hypertonic solutions except in company with the dissolved substances. There is nothing in this inconsistent with Höber's view that certain neutral salts may exert an action on the corpuscles which alters their permeability by altering the physical condition of the colloids in the superficial layer. Nor is there anything inconsistent with my observation that blood charged with ammonium chloride, a substance which readily penetrates the blood corpuscles, is much less easily laked by foreign serum or saponin than normal blood. The circumstance that the foreign serum in this case brings electrolytes (doubtless ammonium chloride) out of the corpuscles in preference to hæmoglobin, whereas normally it brings out hæmoglobin in preference to electrolytes, is instructive. Here we have a corpuscle whose stroma is enriched with a salt which there is reason to believe is not all simply in solution, but partly bound or adsorbed, perhaps in much the same way as the blood pigment itself, but more loosely. The lytic serum increases the permeability of the corpuscles and water enters them. But instead of dissociating the hæmoglobin from the stroma, we may suppose that the water first dissociates the less firmly held salt, which goes into aqueous solution and in this condition easily passes out of the corpuscles. Later on, the water accomplishes the solution of the hæmoglobin, but more slowly and incompletely than in the absence of the salt. The condition of a portion of the ammonium chloride in the corpuscle, seems to be analogous to that of the relatively small amount of electrolytes which escape from the corpuscle with or before the hæmoglobin in the laking of normal corpuscles by the more gentle hæmolytic agents. Some of the ammonium chloride may be more firmly united to the stroma, and saponin produces the same marked increase in conductivity as it does in normal blood.

In Table X of the paper cited,¹³⁶ the conductivity of rabbit's ammonium chloride blood after the action of dog's serum was 106.5. If simple mixture had taken place without redistribution of electrolytes, it

¹³⁶ Journ. of Physiology, xxiv, p 228, 1899.

would have been only 92.3. The difference is not due to mere dilution of the blood with serum, since in Table IX the conductivity of normal rabbit's blood after addition of dog's serum is less than it would have been if simple mixture had taken place, even before escape of the hæmoglobin, probably because electrolytes have entered the corpuscles. When the osmotic equilibrium is upset by the hæmolytic action of the foreign serum the corpuscles, abnormally rich in electrolytes, and in electrolytes which easily penetrate the envelope, lose a portion of their excess, while corpuscles containing the normal electrolytes in normal amount tend at first rather to gain electrolytes from the serum. This agrees very well with the idea that normally the osmotic concentration in the interior of the corpuscles is somewhat less than that of the serum, a condition which may account for the transitory shrinking of the corpuscles in serum hæmolysis observed by Baumgarten.

Hæmolytic experiments on artificial or denatured erythrocytes. In order to study the complicated phenomenon of hæmolysis by eliminating certain of the factors, one may have recourse to corpuscles more or less altered, for instance, to corpuscles fixed in various ways, especially when the nature of the fixative process and the point of attack of the fixing reagent are more or less understood. So far as I am aware, this method was first employed by me.¹³⁷ I used formaldehyde to fix the corpuscles, also heat, osmic acid, and other agents. Matthes¹³⁸ employed corpuscles fixed by Hayem's solution (sublimate) in certain studies on hæmolysis. Sachs¹³⁹ showed that substances like potassium iodide and sodium hyposulphite, which can combine with mercury, will lake sublimate-fixed corpuscles, and that serum, whether heated or not, whether foreign or belonging to the same animal, possesses this property also in virtue of the power of its proteins to unite with the mercury salt and to withdraw it from its combinations in the corpuscles. Von Dungern and Coca¹⁴⁰ have recently announced that osmic-hardened corpuscles can be laked by foreign sera. In formaldehyde fixing, as already mentioned, the erythrocyte is altered so little in certain important respects that we are entitled to look upon corpuscles fixed in this way as cells whose envelopes are still exceed-

¹³⁷ Journ. of Physiology. xxvi, p. 494, 1901.

¹³⁸ Münch. Med. Woch., Jan. 7 and Apr. 29, 1902.

¹³⁹ Ibid., Feb. 4, 1902.

¹⁴⁰ Berlin. Klin. Woch, xlv, p. 1471, 1907.

ingly good imitations of the envelopes of normal corpuscles—much better imitations, it is hardly necessary to say, than those cholesterol-lecithin membranes with which Pascucci worked¹⁴¹ and on which he obtained results of some interest. The hæmoglobin of the formaldehyde-fixed corpuscles is ultimately changed into methæmoglobin. The hæmoglobin molecule is not disrupted with formation of hæmatin if only the amount of formaldehyde necessary for fixation be employed in sufficiently dilute solution, but it is probably precipitated along with the proteins of the stroma.

The formaldehyde-fixed corpuscles are not laked on suspension in distilled water, even on heating, nor by the action of any of the ordinary laking agents, but can be laked by heating in ammoniacal water. Sublimate-fixed corpuscles at a certain stage of fixation do not lake in distilled water at room temperature, but do so in ammoniacal water, and are laked in distilled water on heating. Both in sublimate and in formaldehyde fixation a stage can be found at which apparently only the peripheral portion of the corpuscle has been hardened, the blood pigment in the interior remaining little, if at all, altered. We have, then, in the fixed corpuscle a simplified scheme of an erythrocyte on which we can study certain questions more readily than on the unaltered corpuscles. For instance, the permeability of the corpuscles to various substances can be investigated with the view of determining, uncomplicated by the escape of hæmoglobin or stroma constituents, whether the normal properties of the corpuscle in this regard are retained. I have shown that saponin is fixed by formaldehyde corpuscles from solution at 0° just as by the normal corpuscles. Also that ammonium chloride penetrates the formaldehyde corpuscles and sodium chloride does not or to a much smaller degree, as is also the case in normal corpuscles. Ammonium chloride seems to be retained in a manner similar to that in which it is retained in the normal corpuscle. After the action of saponin, which renders the formaldehyde corpuscle freely permeable to sodium chloride as well as to ammonium chloride, no binding of the latter seems to occur. This is also true of the ghosts of normal corpuscles laked by saponin.

Since formaldehyde corpuscles acted on by saponin are equally per-

¹⁴¹ Loc. cit.

meable to sodium chloride and ammonium chloride, and the saponin action is a surface action, or at any rate is not associated with the setting free of electrolytes in the interior of the corpuscles, the selective permeability of formaldehyde corpuscles for ammonium chloride is largely an affair of the envelope. It is at any rate not due to an action of the formaldehyde or the formaldehyde-protein compounds, since there is no reason to believe that these are acted on by saponin. No difference between sodium chloride and ammonium chloride in the case of heat-laked blood, either mammalian or fowl's, was observed. In the case of saponin-laked and water-laked corpuscles, however, the characteristic difference between sodium chloride and ammonium chloride still persisted, the former shrinking the ghosts, the latter not. The peculiarity of the corpuscles on which the selective permeability depends is therefore a property of the stroma (with its envelope), a property which is destroyed by exposure to the temperature at which heat-laking occurs. But the experiments do not exclude the blood pigment *in situ* from a share in the action.

In the fixed corpuscle the relation of blood pigment to stroma must of course be very different from the normal. But although the combination is artificial, it is none the less interesting to ask the question whether and how liberation of the blood pigment is brought about. The conditions of liberation of the blood pigment when it exists in a more or less known state in the corpuscle may be expected to throw light on the state of the pigment in the normal corpuscle, from which it can be liberated by establishing certain known conditions. The formaldehyde itself, in such concentrations as were used for fixing, causes at first a small amount of laking. During this period the corpuscles can be shown to be more permeable than normal, not only to sodium chloride, but also to ammonium chloride. Later on, as fixing proceeds, the corpuscles again become as impermeable to sodium chloride as normal corpuscles, while still remaining relatively permeable to ammonium chloride. It is probable that the same action of formaldehyde which causes the slight preliminary laking causes the increase of permeability to sodium chloride, an increase of permeability which in the sodium chloride suspensions conspires to increase the hæmolysis by permitting the entrance of water into the corpuscles. When the corpuscles are fully fixed, as has been said,

they are incapable of being laked by ordinary procedures. Yet if the corpuscles be suspended in water and treated with dilute ammonia slow laking occurs at ordinary temperature, while on heating to 60° C. or, indeed, to a lower temperature, rapid and complete liberation of the blood pigment ensues. What is the mechanism of hæmolysis in this case? It might be thought, that the same change occurs as in the normal corpuscles which are hæmolyzed by alkalies. But this is not an ordinary alkali action, for it is obtained far less easily with sodium hydroxide, although sodium hydroxide is a stronger base and lakes ordinary corpuscles in a smaller concentration than ammonia. Nor is it due directly to the action of ammonia on the blood pigment. For both ammonia and sodium hydroxide change the methæmoglobin and alter the color and spectrum of the blood pigment in precisely the same way and with equal ease. Further, the change in the color of the blood pigment is not an essential condition of the laking. For, if after addition of ammonia the corpuscles be washed with water till the washings give no alkaline reaction to litmus, the blood pigment reverts to its original brown color and shows again the spectrum of methæmoglobin. The corpuscles have exactly the appearance of ordinary formaldehyde-fixed corpuscles. They differ essentially however in this,—that they can now be laked completely by heating in water without further addition of ammonia. Either, then, ammonia still remains fixed in some constituents of the corpuscles, although not affecting the blood pigment, or it has produced a change in some of the corpuscular constituents which is permanent after the excess of ammonia has been washed out. When formaldehyde corpuscles are tested at intervals during the process of fixation, it is found that at first they are easily laked in water alone at ordinary temperature. Later on water does not cause laking at the ordinary temperature, but does so when the temperature is raised. It is not necessary that the temperature should be raised to that of heat-laking of unfixed blood corpuscles. Complete liberation of blood pigment has been obtained at 40° C. in a few minutes. Still later the corpuscles become incapable of being laked in water at any temperature. At this stage the addition of ammonia will cause laking in water at the ordinary temperature. At a still later stage in the fixation process not only must ammonia be added, but the temperature must be raised in order to obtain libera-

tion of the blood pigment. Finally even ammonia and heat will only cause swelling and paling of the corpuscles without liberation of the pigment. At this stage ammonia still easily penetrates the corpuscles as is shown by the instant change in color from brown to red when it is added. For a considerable time, as fixation goes on, although the color of the suspension is distinctly brown, the spectrum shows strong oxyhæmoglobin bands along with a methæmoglobin band in the red of moderate strength. The cautious addition of ammonia causes the band in the red to disappear without any effect on the oxyhæmoglobin bands. If more ammonia be added, a new band makes its appearance just to the left of the D line. The most likely interpretation of these appearances is that the formaldehyde, penetrating into the corpuscles, first changes the more superficial portion of the blood pigment into methæmoglobin, while the interior portion for a time remains unchanged. If this be true, then at this stage we have a corpuscle in whose interior the normal blood pigment still exists, but is not liberated by the action of water because water cannot now produce the changes in the external layer associated with the water-laking of the normal corpuscle. In other words, the partially fixed formaldehyde corpuscle is an instance of a corpuscle protected against ordinary laking agents by an alteration in the superficial layer. If, now, at a sufficiently early stage of fixation, we act on the corpuscle by ammonia, it is restored as regards water-laking to the position of a normal corpuscle. The ammonia in this case affects the partially fixed peripheral layer of the corpuscle in two ways: (1) increasing its permeability for water; (2) altering the methæmoglobin. It is not the change of methæmoglobin into alkaline methæmoglobin which is the important thing, since after washing away the ammonia the brown color is restored and yet the reaction of the corpuscles to water is just the same as if ammonia was still present in sufficient quantity to give the typical red color. One important effect of ammonia is, therefore, the alteration of the permeability of the superficial layer. The relation of the methæmoglobin to the stroma or its solubility may also have been altered.

Some light is thrown on this point by experiments in which blood was rubbed up with sand at various stages of fixation by formaldehyde. It is known that when fresh blood is triturated in this way

laking is produced, apparently because the mechanical changes in the corpuscles permit the entrance of water from the serum. When formaldehyde-fixed blood is rubbed up at a time when laking can still be caused on heating after the addition of ammoniacal water, no evidence can be obtained that any of the blood pigment goes into solution, although the microscope reveals the fragments of numerous broken-down corpuscles. The opportunity has been offered to the serum of dissolving the blood pigment if it were in a condition to enter into aqueous solution. Since it has not done so, we must assume that at this stage it is already insoluble in water or such saline solutions as serum. A part of the ammonia action therefore in laking formaldehyde-fixed corpuscles must be an alteration in the solubility of the blood pigment or in its relation to the stroma. In other words, ammonia not only produces a change in the permeability of the corpuscle, but it unfixes the stroma constituents or the blood pigment.

As to the chemical or physical changes produced by the ammonia, we can assume that in part they are the same as those which lead to the laking of unfixed corpuscles, alkalies being laking agents in virtue of their action on the colloids, forming compounds for example with lecithin¹⁴² and with nucleo-histon.¹⁴³ But in addition we must assume that ammonia has a special action in breaking up compounds which formaldehyde forms with protein. The decidedly smaller effect of sodium hydrate in favoring liberation of the blood pigment from formaldehyde corpuscles speaks in this sense.

F. Blum¹⁴⁴ came to the conclusion that the combinations of formaldehyde with proteins can be considered as methylene derivatives. Benedicenti¹⁴⁵ repeated and extended the observations of Blum, using various proteins and gelatin. He concluded that the formaldehyde-protein compounds are formed by a parallel process to the known reactions of aldehydes on ammonia and the amido-compounds, the point of attack in the protein molecule being the N-containing groups. If aldehydes are brought into contact with ammonia, in general aldehyde-ammonias are

¹⁴² W. Koch, loc. cit.

¹⁴³ For the reactions of nucleohistons and histons which bear on our subject, see Samuely, in Oppenheimer's *Handbuch der Biochemie*, i, p. 308, 1908.

¹⁴⁴ *Anatomischer Anzeiger*, vol. xi, p. 718, 1895; *Zeit. für Physiol. Chem.*, xx, p. 127, 1896.

¹⁴⁵ *Archiv für Anat. u. Physiologie*, p. 219, 1897

formed, a series of compounds which have the empirical composition represented by the addition of a molecule of ammonia to a molecule of aldehyde. These are unstable compounds, and tend easily to either decompose again into their components or to polymerize with loss of water. Thus as the final result of the action of ammonia on formaldehyde we obtain a base usually termed hexamethylenetetramine ($C_6H_{12}N_4$), which, on heating with acids, is easily split into formaldehyde and ammonia. It is partially decomposed into these substances even in neutral watery solutions above $50^\circ C$.¹⁴⁶ Of the reactions of formaldehyde with amido-compounds, the most interesting in connection with our subject is that with urea. This compound easily splits up, giving off formaldehyde.

Schwarz¹⁴⁷ investigated the action of a series of aldehydes, including formaldehyde, on crystallized egg albumin and serum albumin, serum globulin and heteroalbumose, and concluded that the formaldehyde compounds are to be considered as methylene derivatives of the otherwise unaltered protein molecule. Benedicenti¹⁴⁸ found that casein treated with formaldehyde binds less hydrochloric acid after treatment than normal casein. It becomes quite incapable of swelling in hydrochloric acid and indigestible by pepsin or trypsin. But, according to Schwarz, pepsin-hydrochloric acid will digest the formaldehyde-protein compounds studied by him although trypsin will not, the difference being probably due to the hydrochloric acid splitting off the aldehydes and thus freeing the points of attack of the pepsin on the protein molecule. The compounds which the formaldehyde forms with protein can be broken up by steam, all the formaldehyde being recovered on distillation. Gelatin hardened by formaldehyde regains its normal solubility on getting rid of the formaldehyde by steam. The serum-albumin formaldehyde compound is precipitated by various salts, including mercuric chloride (Schwarz). On ammonium salts formaldehyde acts in a different way than on ammonia. On heating formaldehyde and an ammonium salt under pressure, the ammonia is changed successively into mono- di- and trimethylamine¹⁴⁹.

Sollmann¹⁵⁰ has shown that when the alkalinity passes a certain grade

¹⁴⁶ Meyer and Jacobson, *Lehrbuch der Organischen Chemie*, 2d Aufl., Bd. i, p. 749, Leipzig, 1907.

¹⁴⁷ *Zeit. für physiol. Chem.*, xxxi, p. 460, 1900.

¹⁴⁸ *Loc. cit.*

¹⁴⁹ Meyer and Jacobson, *loc. cit.*

¹⁵⁰ *Amer. Journ. of Physiology*, vii, p. 220, 1902.

the precipitate formed by formaldehyde in a weakly alkaline solution of Witte's peptone is redissolved.

Certain of these reactions, if they take place in formaldehyde corpuscles, would help to explain their peculiar behavior. Unfixing of the corpuscle, to the extent that the blood pigment is set free from its combination with the stroma, may be due to the union of the ammonia with the formaldehyde. Solution of the hæmoglobin may be related to the fact that ammonia in the slightest excess dissolves globin. It is known that the presence of salts hinders the laking action of alkalies on unfixed corpuscles. The influence of ammonium salts on ammonia laking is especially great.¹⁵¹ The inhibitory action of ammonium chloride on the laking of formaldehyde corpuscles by ammonia may be accounted for by the hindering effect of ammonium salts on the solution of globin by ammonia. If formaldehyde fixes any constituents of the envelope, the unlocking of these combinations, especially when the temperature is raised, may be expected to increase the permeability of the corpuscle to water. and the presence of excess of water in the interior of the corpuscle which is indicated by its swelling before laking will, of course, favor the solution of blood pigment, which, even after the breaking up of the formaldehyde-protein compounds of the stroma, may still be bound to stroma constituents. In this connection the restoration of the power of imbibition of protein previously treated with formaldehyde when subjected to the action of steam,¹⁵² is of special interest. The favoring action of urea solutions on ammonia laking of formaldehyde corpuscles is to be explained partly by the reaction of urea with formaldehyde mentioned above, partly by the water action of an aqueous solution of a substance like urea which readily penetrates the corpuscles.

In blood partially fixed by formaldehyde and laked by saponin the ghosts are not broken up by water, as is the case in ordinary blood laked by saponin. The explanation is that while saponin still dissolves lipoids in the ghost, it does not dissolve the protein. Therefore the saponin alone does not destroy the ghost. Nor does the water admitted by the saponin action from the serum or from the suspending sodium chloride solution, or water added to the suspending liquid in

¹⁵¹ Arrhenius, *The Chemistry of Immunity*, p. 110, 1907.

¹⁵² Benedicenti, *loc. cit.*

excess, dissolve the nucleo-protein, since it has been sufficiently fixed by formaldehyde. In unfixed corpuscles laked by saponin and then treated with water, the saponin dissolves the lipoids of the ghosts and the water alters the nucleo-protein so that the ghosts disappear.

The laking of sublimate-fixed corpuscles by heating in water to a temperature not higher than that of heat-laking of unfixed corpuscles is an interesting phenomenon. The liberation of the hæmoglobin is rapid and complete. The ghosts remain remarkably distinct and can be filtered off practically without loss. The laking is prevented by hypertonic sodium chloride solution. Mann's conclusion¹⁵³ that "when a protein coagulated by sublimate is treated with a solution of sodium chloride, it becomes soluble" is difficult to understand in view of the fact that sodium chloride prevents the laking of sublimate-fixed corpuscles by heat, unless we assume that the action of the sodium chloride is an osmotic one, water being unable to enter the corpuscle from the sodium chloride solution. Yet, after treatment with 10 per cent sodium chloride solution laking does not take place even on heating with distilled water, possibly because the sodium chloride has precipitated nucleo-histon. Sodium chloride precipitates neutral salts of histon, while mercuric chloride does not precipitate histons.¹⁵⁴ In the corpuscles, some of whose constituents have been fixed by mercuric chloride, the additional action of sodium chloride may be sufficient to determine a change which prevents subsequent laking, although the sodium chloride itself does not prevent the laking of normal corpuscles. Laking of a watery suspension of sublimate-fixed corpuscles by amyl alcohol is also prevented by treatment with 0.9 per cent sodium chloride solution. After the action of 10 per cent sodium chloride, even ammonium sulphide will not lake sublimate corpuscles.

If, at the stage of sublimate fixation where laking is readily produced by heating in water at 55° C., the fixed corpuscles suspended in water be rubbed up with sand at room temperature, no blood pigment goes into solution, although the corpuscles are seen under the microscope to have been broken down in large numbers to a granular débris. In the interior of the corpuscle, then, at this stage none of the pigment is in a water-soluble state. Yet it can be shown by spectroscopic

¹⁵³ Chemistry of the Proteids, p. 313.

¹⁵⁴ Oppenheimer's Handbuch, loc. cit.

examination that much of it is still so little altered that it gives the oxyhæmoglobin bands. This is illustrated by the following excerpt from the protocols:

March 2, 1909. Added to ox-blood an equal volume of 4 per cent formaldehyde solution (in 0.9 per cent sodium chloride). To another portion of the blood added one-fourth of its volume of a saturated aqueous solution of mercuric chloride. Kept in cool room.

March 4. Centrifuged some of the sublimate blood, which has a brown color, and a spectrum with a good (methæmoglobin) band in the red and two strong oxyhæmoglobin bands. Some blood pigment is in solution in the superjacent liquid. This liquid shows a spectrum with a strong band in the red in position of methæmoglobin band and two fainter bands in position of oxyhæmoglobin bands. On addition of ammonia to the liquid the band in the red disappears, and the band of alkaline methæmoglobin just to the left of D appears. The two other bands persist. Added ammonia to some of the sublimate blood. It laves immediately, and then shows no band in the red. The oxyhæmoglobin bands remain unchanged and very strong, and there is a fainter band just to the left of D. On comparison of the spectra of the superjacent liquid and the laked blood after addition of ammonia, the following differences are noted: (1) When the two liquids are made of approximately equal strength the oxyhæmoglobin bands are much stronger in the laked blood. (2) On diluting the laked blood till the tint is considerably weaker than that of the superjacent liquid, the band immediately to the left of D disappears, while the oxyhæmoglobin bands are still quite markedly stronger than in the superjacent liquid. (3) The tint of the diluted superjacent liquid when held against the sky has a distinct brownish element in it; that of the diluted laked blood is much more nearly a pure red. The explanation probably is that in the interior of the corpuscles there is still much unaltered blood pigment, or at any rate blood pigment so little altered that it still gives the oxyhæmoglobin spectrum, even if it is united in some way to the mercury salt. The blood pigment liberated in the superjacent liquid is of course more profoundly altered by the sublimate. The brown color of the corpuscles is probably due to the alteration of the pigment in the more superficial portions of the corpuscle. That the bands in the position of the oxyhæmoglobin bands are not those of so-called alkaline methæmoglobin was shown by observing the spectrum, while ammonia was pipetted on to the blood in the parallel-sided trough. No change took place in the bands.

The most probable conclusion is that heating causes a change in some of the other constituents of the corpuscle than the blood pigment, which permits the pigment to go into solution and escape. This change is probably not essentially different from that which takes place in the heat laking of ordinary corpuscles. The common statement¹⁵⁵ is that mercuric chloride does not precipitate oxyhæmoglobin till the oxyhæmoglobin is decomposed and has become brown owing to the formation of hæmatin. If this is correct we must assume that in the partially fixed sublimate corpuscles, at the stage mentioned, the undecomposed oxyhæmoglobin is prevented from going into solution when the corpuscles are triturated with water because the mercury salt has fixed some constituents of the stroma. Either the precipitation of these constituents throughout the whole substance of the stroma mechanically prevents the water from dissolving the oxyhæmoglobin, which seems quite improbable, or the mercuric chloride, by uniting with the stroma constituent of the hæmochrome complex, renders the hæmochrome insoluble to water without essentially altering its spectrum.

Permeability of the nucleus and its relation to hæmolysis. The nuclear membrane and the envelope of the corpuscle have each their special properties. They are not in general affected equally nor in the same sense by a given agent. Great swelling of the nucleus can be produced while the corpuscles remain of approximately normal size, and great swelling of the corpuscle without marked change in the size of the nucleus. The fact that methylene blue stains the nuclear membrane as a rule more deeply than the envelope of the corpuscle suggests that the quantity of protein in the former is greater. Bing and Ellermann¹⁵⁶ have shown that in the staining of the medullary sheath with methylene blue, the absence of the lipoids does not affect the result.

The absence of swelling of the nuclei of *Necturus* corpuscles fixed by formaldehyde and then laked by ammonia perhaps indicates that the nucleus or the nuclear membrane is richer in nucleo-histons and less rich in lipoids than the envelope and the stroma of the corpuscle. The same explanation may be given for the osmic acid corpuscles, which swell on heating in ammoniacal water, while the nucleus does not.

¹⁵⁵ Gamgee in Schäfer's Text-book of Physiology, i, p. 207.

¹⁵⁶ Archiv für Anat. u. Physiol., p. 256, 1901.

On the other hand, the Necturus corpuscles fixed by Hayem's solution when laked by water and ammonia show swelling of the nucleus, possibly because ammonium chloride does not precipitate histon¹⁵⁷ so that the nucleus is in a position to swell on addition of ammonia. Ammonium salts of nucleo-histons are soluble in water, and therefore the nuclear membrane after the action of ammonia admits water easily. Sulphuretted hydrogen added to sublimate corpuscles causes laking at the ordinary temperature without swelling of the nucleus or change in the intranuclear network. Therefore, the constituents of the nucleus or of the nuclear membrane which has been acted upon by the mercury salt are either more firmly fixed by it than the constituents of the corpuscular envelope and stroma, or the breaking up of their mercury compounds leaves them relatively unaffected as regards their osmotic properties. The fact that sapotoxin does not cause swelling of the nucleus when it lakes Necturus corpuscles, although it removes some of the stain from the nuclei of heat-laked ghosts stained with methylene blue also suggests that lipoids are not so important in the nuclear membrane as in the cell envelope,

Sodium taurocholate does not at first swell the nuclei of Necturus corpuscles, although later on they become swollen, possibly by a water action owing to the great increase in water in the contents of the corpuscle. This conclusion is supported by the fact that urea solution (1 per cent) causes swelling of the nucleus as well as of the corpuscle, doubtless because urea easily penetrates both, and water itself has the same effect. The taurocholate usually does not cause swelling of the corpuscles, in which case the excess of water in the corpuscles necessary for the swelling of the nucleus does not exist, unless the blood pigment has been already discharged and its place occupied by water.

It is unnecessary to labor the point that the permeability of the nucleus is different from that of the corpuscle. For example, ammonium chloride is taken up greedily by the extranuclear portion of the hen's corpuscle, but not by the nucleus.¹⁵⁸ This difference is certainly due in part to a difference in the properties of the nuclear and corpuscular envelopes. But it may be partly due to a difference in the contents of the two structures.

¹⁵⁷ Samuely, loc. cit.

¹⁵⁸ Amer. Journ. of Physiol., viii, p. 107, 1902.

Classification of laking agents. This paper is concerned with the more general aspects of hæmolysis and does not deal in detail with all the very numerous laking agents. Certain points, however, in connection with the mechanism of laking by some of the groups into which hæmolytic agents can be divided, may now be summarized.

Laking may be brought about by (1) mechanical means (pressure, trituration, shaking); (2) physical changes (freezing and thawing, heat, condensor discharges, water, drying and subsequent exposure to salt solutions); (3) chemical agents (saponin, bile salts, ether, chloroform, acids, alkalis, etc.); (4) biological agents (the specific hæmolysins, bacterial hæmolysins—including the bodies active in putrefactive hæmolysis, spontaneous laking, autolysis).

This classification is not a strict one, although it is useful for purposes of description. It is quite probable, for example, that interchange of water between the corpuscles and the suspending liquid is produced by the first group and that chemical changes are produced by the second. On the other hand, physical effects are unquestionably concerned in the action of such reagents as saponin, which dissolves cholesterin and lecithin. In biological hæmolysis properly so called both chemical and physical reactions are also in all probability concerned.

Mechanical Laking. Possibly the laking produced by shaking is due to a precipitation of some of the colloids of the corpuscles like the precipitation of albumin and other proteins studied by Ramsden. The laking produced by rubbing up with sand may be due to the alteration of the envelope or stroma in such a way as to permit the entrance of some water into the corpuscle. Yet it differs from the ordinary water laking in this, that the conductivity of the laked blood is but little increased, and the action of saponin on the ghosts causes a great further increase of conductivity. Another factor in the laking by trituration may be mechanical squeezing of a certain amount of water out of the corpuscles, leading to a more labile condition of the blood pigment in them analogous to that observed by Peskind,¹⁵⁹ who saw that after the precipitation of corpuscles by slight excess of acid salts (ammonium ferrous sulphate) pressure on the cover slip caused the blood pigment

¹⁵⁹ Amer. Journ. of Physiol., viii, p. 411, 1903.

to pass out, leaving almost colorless shadows. The intraglobular crystallization produced by abstraction of water from the corpuscles of fishes' blood by hypertonic solutions of salts¹⁶⁰ is perhaps a similar phenomenon.

The conclusion that the amount of trituration necessary to liberate all the blood pigment does not alter the stroma so profoundly as water does is corroborated by an observation of Belonowski.¹⁶¹ Working with the spider poison (arachnolysin) he found that the stromata of corpuscles of a species sensitive to the toxin, after laking by rubbing up the blood with sand and decanting off the serum, have a much greater binding power for the toxin than stromata obtained by the method of Sachs (heating to the temperature of heat-laking and treatment with 6 to 10 volumes of water) or by the method of Pascucci, in which treatment with excess of water is also a step.

Heat-Laking.—Reasons have already been given why this cannot be considered as due merely to the melting of fatty constituents of the corpuscles at a definite temperature. There is every reason to believe, however, that combinations containing lipoids are disrupted under the favoring influence of heat once a certain critical temperature has been passed. The stromata do not entirely lose their semi-permeable properties, as they do if the temperature is raised to the coagulation point of the serum proteins. Nor in careful heat laking are the electrolytes liberated from the stromata in such quantity as in violent methods of laking like saponin or water laking. Laking by condenser discharges, which according to Rollett¹⁶² does not cause liberation of the electrolytes along with the hæmoglobin, may very well be a form of heat laking, as Cremer¹⁶³ suggests, due to local heating of the badly conducting envelopes of the corpuscles.

Laking of Dried Corpuscles.—After the loss of a certain amount of water, as has been shown by me,¹⁶⁴ and in greater detail by my pupil, Prof. C. C. Guthrie,¹⁶⁵ the erythrocytes are laked by isotonic or even

¹⁶⁰ Hamburger, Osmotischer Druck I.

¹⁶¹ Bio-chem. Zeit., v, p. 65, 1907.

¹⁶² Pflüger's Archiv, lxxxii, p. 199, 1900.

¹⁶³ Zeit. für Biol., xlv, p. 101, 1904.

¹⁶⁴ American Journ. of Physiology, viii, p. 117, 1902.

¹⁶⁵ Ibid., p. 441, 1903.

by hypotonic salt solutions, and by their own serum. The permeability of the corpuscles is radically altered by drying at air temperature, so that dried corpuscles are far less normal in their osmotic relations than formaldehyde-fixed corpuscles. Doubtless this is a reason why corpuscles fixed by any process in which drying of smears is a step stain better than moist corpuscles. Heat fixation causes also a great increase in the permeability. It follows from this that fixed corpuscles which have been subjected to drying or heating before fixation are unsuitable for experiments on permeability, although they have sometimes been employed, for instance in the study of the permeability of the corpuscles for dyes. It is easy to see that the loss of a certain amount of water may upset the equilibrium of the colloid solutions in the corpuscles, leading it may be to precipitation of proteins and other colloids in the envelope or in the interior of the stroma. ~

Laking by Chemical Agents.—A noteworthy circumstance in laking by these agents is that a certain amount, even of those which very easily penetrate the corpuscles, must be taken up before any hæmoglobin whatever is liberated. Thus ethyl alcohol, dissolved to the extent of 10 per cent by volume in 1 per cent sodium chloride solution, does not cause the least laking in twenty-four hours in the cold, although the blood is still rapidly laked by addition of more alcohol or by water.¹⁶⁶

Laking by Foreign Serum.—According to Arrhenius¹⁶⁷ the immune body (amboceptor) is not chemically bound by the erythrocytes. Perhaps it is taken up by a surface action (adsorption). For, (1), like saponin, it is readily taken up at 0° C., that is, the temperature coefficient is small. Now, saponin produces at 0° C. almost as great an increase in the conductivity of formaldehyde corpuscles as at ordinary temperature, and therefore its action may be supposed to be largely a surface action. (2) The amboceptor is relatively thermostable, and so is the agglutinin, which certainly has a surface action as a fundamental part of its effect. (3) As already mentioned, substances which give rise to the production of specific hæmolysins and agglutinins are still present in the active condition in formaldehyde corpuscles. Now, according to Bang and Forssman¹⁶⁸ the hæmoly-

¹⁶⁶ Journ. of Med. Research., loc. cit., p. 304.

¹⁶⁷ Chemistry of Immunity, 1907.

¹⁶⁸ Hofmeister's Beiträge, viii, p. 238, 1906.

sinogens are substances which can be extracted by ether and similar solvents, and we know that the extraction of ether-soluble substances from formaldehyde corpuscles produces a change in the surface layer. Therefore, probably hæmolysinogenic substance (antigen) is present in the surface layer of the corpuscle. So that if the substance in the corpuscle which fixes hæmolysin (amboceptor) is identical with hæmolysinogen or related to it, the amboceptor action might be expected to be an action on the surface of the corpuscle. (4) The surface being altered by the amboceptor, the complement may gain admittance by some reaction with a much greater temperature coefficient than that concerned in taking up the amboceptor, a reaction perhaps due to ordinary chemical affinity. The permeability of the corpuscle to water need not be materially increased by the amboceptor (absence of laking in corpuscles charged with amboceptor alone).

The complement when fixed may determine the increase of permeability to water and also the loosening of the bonds between the stroma and the hæmochrome. Instead of activation of the complement by amboceptor in the serum, the amboceptor at the temperature at which laking takes place may be rapidly adsorbed, and the complement more slowly, giving rise to gradual laking. Arrhenius believes that a union of amboceptor and complement takes place in the interior of the corpuscle. Yet that some change occurs in the permeability of corpuscles under the influence of amboceptor alone is indicated by the fact that the conductivity of rabbit's blood treated with dog's serum after inactivation by heat is not the same as it would have been had a similar quantity of an indifferent salt solution been added to the blood instead of the dog's serum, but is distinctly less than this. It is interesting that in blood artificially enriched with ammonium chloride, foreign serum inactivated by heating to 60° produces a change in conductivity in the same sense as the unheated serum, although not so marked, that is, in the opposite sense to the change produced by foreign serum in the case of normal blood. Thus in Table X¹⁰⁹ the conductivity of the mixture of heated dog's serum and ammonium chloride rabbit's blood was 101.4, whereas, if simple mixture had taken place it would have only been 91.5. The same explanation may be given of the difference as on page 78.

¹⁰⁹ Journ. of Physiol., xxiv, p. 228.

In this connection we might think of J. Traube's statement,¹⁷⁰ that the surface tension of serum is diminished by heating to 56° by the formation of substances which are adsorbed or dissolved in lipoids in the presence of red corpuscles. He suggests that in this way the envelopes of the corpuscles are thickened and that this thickening hinders hæmolysis, although it does not hinder the attachment of the amboceptor. This idea, however, does not explain the phenomenon we have been discussing. For although a corpuscle with a thickened envelope might be expected to be even less permeable to serum ions than a normal corpuscle, the normal corpuscle is such a bad conductor that no possible diminution in its conductivity could produce so distinct a diminution in the conductivity of the suspension as was observed. It is possible that the agglutinin plays some part in this change. Even in the case of so energetic a laking agent as water, one has observed that the agglutination produced by it need not entail the entrance of water and consequent swelling of corpuscles. Crenated corpuscles can agglutinate. Laking by water, however, is always preceded by swelling of the corpuscles.

Possibly the substances responsible for Traube's phenomenon are the same as cause the increase of alkalinity of serum inactivated by heat observed by Liebermann¹⁷¹ and confirmed by Seligmann.¹⁷²

The Influence of Cane-sugar on Serum Laking.—It has been shown that this form of hæmolysis is inhibited by cane-sugar. What is the mechanism of this action? In one experiment¹⁷³ a cane-sugar solution slightly hypertonic was used. This would cause slight dilution of the serum and therefore a small diminution of its specific conductivity. In the case of the heated serum the conductivity of the liquid removed after action on the rabbit's corpuscles was 49.13. The conductivity of the liquid calculated on the assumption that simple mixture had taken place is 50.3. No hæmoglobin was in solution. For the blood mixed with heated serum the conductivity was exactly the same as the calculated conductivity. This agrees well with the assumption that in presence of cane-sugar no change occurred in the distribution of

¹⁷⁰ Bio-chem. Zeit., x, p. 380, 1908.

¹⁷¹ Archiv für Hygiene, lxii, 1907.

¹⁷² Bio-chem. Zeit., x, p. 430, 1908.

¹⁷³ Journ. of Med. Research, viii, p. 302.

serum ions. The slight diminution of conductivity of the extra-corpuscular liquid would be made up in the case of the blood by a widening of the conduction paths through the slight shrinking of the corpuscles. Either then the amboceptor is not fixed by the corpuscles in the presence of cane-sugar, which is negatived by the fact that with unheated serum some laking occurs, or the fixing of the amboceptor does not produce that change in the corpuscles in the presence of sugar which permits water and electrolytes to enter them, as occurs in the case of dog's serum (unheated and heated) acting on rabbit's corpuscles in the absence of sugar. It is easy to see that the presence of sugar which could not enter the corpuscles might prevent water and salts from entering them. For if we suppose that the corpuscles and serum are in equilibrium at the outset, and that the amboceptor renders the envelope more permeable to salts, the salt must in entering the corpuscles be accompanied by a corresponding amount of water. Otherwise the osmotic pressure in the corpuscles would be increased and that outside the corpuscles diminished. The difference of pressure would bring the entrance of salts into the corpuscles to an end, or water must accompany them.

Spontaneous Laking.—The so-called spontaneous laking, *i.e.*, the laking which takes place when blood is preserved in sterile tubes (or in the cavities of sterile paraffine) is possibly an autolytic process¹⁷⁴ due to ferments developed in the erythrocytes themselves, or to ferments derived from the leucocytes or the serum, or to the action of bodies produced by the autolysis of the serum proteins or other constituents of the blood. The conductivity and Δ of the laked blood, at first altered but little, are ultimately increased very greatly, although far less than when putrefaction is allowed to take place.¹⁷⁵ Precisely similar observations have since been published by Oker Blom,¹⁷⁶ by Buglia¹⁷⁷ and by Polimanti.¹⁷⁸

¹⁷⁴ Stewart, Amer. Journ. of Phys., xi, p. 374, 1904.

¹⁷⁵ Stewart, Journ. of Exp. Med., iv, p. 235, 1899.

¹⁷⁶ Skand: Archiv, xiv, p. 48, 1903.

¹⁷⁷ Archivio di Fisiologia, iv, p. 56, 1906.

¹⁷⁸ Bio-chem. Zeit., xi, p. 260, 1908.

SUMMARY

The mechanism of hæmolysis is investigated from the standpoint of the relation of the physico-chemical properties of the erythrocytes to their histological structure.

Evidence, both histological and physico-chemical, is brought forward that the superficial layer (envelope) of the erythrocyte plays an important part in regulating the exchange between the corpuscles and the plasma or other suspending liquid, and that alterations in this layer have an influence, often decisive, in causing liberation of the blood pigment. The alterations of the envelope, however, do not directly permit escape of the pigment, but merely allow the conditions to be established which are necessary for the transformation of the hæmochrome (the native blood pigment). This is probably present in the corpuscle in combination with stroma constituents in the form of a gel. When water passes into the erythrocyte through the altered envelope, or when in addition the hæmolytic agent acts upon the hæmochrome-stroma complex, the hæmochrome gel is transformed into an aqueous solution of hæmoglobin in the interior of the corpuscle. An aqueous solution of hæmoglobin, present now for the first time in the history of the erythrocyte, acts upon it as a foreign body, and indeed as a foreign body having itself hæmolytic powers. Once formed, the hæmoglobin solution passes out through the envelope, which has no affinity for the blood pigment, and is itself, in the intact corpuscle, free from pigment. In the more gentle methods of laking the transformation of hæmochrome into hæmoglobin solution is due partly to the action of the water which enters the corpuscle when its permeability is altered by the hæmolytic agent. When laking is accomplished by more violent methods the direct action of the hæmolytic substance on the hæmochrome-stroma complex is also an influential factor, in addition to the water action. This direct action is, of course, not excluded even in the gentlest methods of laking. Hæmochromolysis, the change of the hæmochrome into hæmoglobin in aqueous solution, may be distinguished from stromatolysis, the more profound alteration of the stroma. The former is accompanied by a relatively small and the latter by a relatively large escape of electrolytes from the corpuscles. These electrolytes are in part

set free from combinations or adsorptates with colloids, but in part escape simply because of the altered permeability of the corpuscle.

Some evidence is offered that the electrolytes of the erythrocytes may be divided into three fractions: a portion which escapes with even the gentlest methods of laking, a portion liberated only by energetic laking agents, and a portion only set free by such destructive processes as incineration. The hypothesis that the first fraction is in solution, the second in loose combination (or adsorbed), the third more firmly combined, has a certain plausibility. But it has not been proved that the liberation of the second fraction, or a part of it, may not be due merely to a change in the permeability of the corpuscle.

NOTE.—The interpretation placed upon Gamgee's results in the footnote on p. 60 seems to be the proper one. His statement (referring to my paper in *Journal of Physiology*, xxiv, p. 356, 1899) that "although solution of oxy-hæmoglobin possess a low conductivity, this is very much higher than has been found in the previous observations of Stewart," shows that either his oxy-hæmoglobin or his distilled water was less thoroughly freed from electrolytes than mine. In observations of this kind the error must appear as too high and not as too low a conductivity.

COLLOID GLANDS (GOITRES): THEIR ETIOLOGY AND PHYSIOLOGICAL SIGNIFICANCE.¹

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Our object in this paper is to present certain data concerning the production, the anatomical and the physiological status of uncomplicated colloid glands (goitres). These observations have been made upon sheep's and dogs' thyroids, and though still incomplete, they tend to modify to some extent the generally held opinions as to the exact place in pathology which colloid glands should occupy.

Before taking up these data it may be well to mention briefly the great anatomical groupings that one has to deal with in establishing a point of departure for the study of the processes involved. These are four, viz: (1) Normal glands; (2) Colloid glands (goitres, all degrees); (3) Hyperplastic thyroids (all degrees); (4) Complications (engrafted on any of the three preceding groups). Barring *atrophies*, *neoplasms* and *infections*, all thyroids naturally fall into one or another of these four groups. Leaving out of consideration the last group (complications), for we are not concerned with them here, the anatomical characteristics of the remaining groups are well defined and generally known. (Johns Hopkins Hospital Bulletin, 1907, XVIII, 359.)

The literature dealing with colloid glands (goitres) is highly complicated, and for very sufficient reasons: First, it

¹ Presented in abstract at the meeting of the American Association of Pathologists and Bacteriologists, Ann Arbor, Mich., April 17, 1908.

[131] has dealt almost entirely with human material, and, as is well known, most operative specimens show one or more secondary changes (complications). It is due to this fact in particular that existing classifications of goitres include such terms as cystic, calcareous, fibrous, vascular, gelatinous, etc. These terms, it seems, should not be raised to primary importance since, as Virchow (*Die krankhaften Geschwülste*, III, 4) has pointed out, they are only examples of complications engrafted on a more fundamental type of change. Probably the essential reason why we do not find any very definite description of colloid glands (goitres) in the literature is because their comparative and experimental pathology has been but little developed and it is only in the lower animals that we are able to study uncomplicated forms in series.

In this discussion of colloid glands (goitres) we are using [132] the term "goitre" parenthetically for the following reasons:

(1) In the older literature of human pathology other cervical enlargements than those of the thyroid have been described as goitre; (2) The term has been applied to a great variety of thyroid enlargements, viz: cysts, foetal adenomata, malignant tumors and inflammatory swellings, etc.; (3) Goitre is primarily a clinical term; (4) There is a growing tendency, and rightly we think, to include under the term goitre the entire group of anatomical changes of which the major ones are those of the thyroid (hyperplasia) and lymphoid tissues (spleen, thymus and lymph glands). (Marie: *Gaz. d. Hôp.*, 1893, 202; Hektoen: *Internat. Med. Mag.*, 1895-6, IV, 584; Kocher: *Arch. f. klin. Chir.*, 1908, LXXXVII, 131; Caro: *Berl. klin. Wehnschr.*, 1907, XLIV, 519; Boit: *Frankfurt. Ztschr. f. Path.*, Bd. I, 187; Hirschlaff: *Deutsche Ztschr. f. klin. Med.*, 1899, XXXVI, 200; Hart: *München. med. Wehnschr.*, 1908, LV, Nos. 13 and 14.)

Since thyroids frequently show quite marked degrees of hyperplasia without being noticeable clinically (the preclinical stage of goitre), and also since there may be distinct anatomical evidences of a previous active hyperplasia in a gland now rich in colloid, although the gland clinically or macroscopically is not enlarged, it might be confusing to use the word "goitre" unguardedly. Thus we include under the term

colloid glands (goitres) all glands which show histological evidence of reversion from any degree of previous active hyperplasia irrespective of the size of the glands. [132]

Brief mention has already been made in previous papers (Johns Hopkins Hospital Bulletin, 1907, XVIII, 359; Arch. of Int. Med., 1908, I, 349) of the incidence and nature of the anatomical changes that occur in thyroids undergoing active hyperplasia, one sequence of which is the production of colloid glands (goitres). We have called this change "reversion" because it seemed to us from the observed phenomena in animals that the changes were best interpreted as the return of the hyperplasia to a more normal type of gland.

The data which follow are presented somewhat in the order of their observation and will be discussed under the following headings: (1) Anatomical changes; (2) Age of the animals; (3) Inconstant changes following the removal of one lobe of the thyroid and the possibility of other factors than quantity of thyroid influencing thyroid changes; (4) More direct evidence of some additional factors determining thyroid hyperplasia, and reversion; (5) Effect of administration of iodine, the relation of iodine to gland structure, etc.; (6) Comparison of the general biological reactions of colloid and of normal glands; (7) The preventive effect of iodine on secondary hyperplasia; (8) Summary.

1. ANATOMICAL CHANGES.

In the routine histological examination of seven hundred (700) dogs' thyroids several examples of colloid glands (goitres) were met with—some complicated, others in pure form. We also observed what appeared to us to be transitional forms, *i. e.*, forms partaking both of the characteristics of colloid glands (goitres) and of active hyperplasias. By arranging these in series with the pure colloids at one end, and the active hyperplasias at the other, the gradations could easily be traced step by step by means of certain common features. *First*, in all specimens there were infoldings and plications of the lining epithelium of the alveoli which in the pure colloid glands appeared as twigs covered with the flat cubical epithelium characteristic of that lining the alveolar

[132] walls proper. In the transitional forms these same infoldings and plications were covered with higher forms of epithelium ranging up to columnar, which also conformed to that of the ruling type of epithelial cells lining the alveolar walls proper. In the pure active hyperplasias the infoldings as well as the alveolar walls proper were always covered with columnar epithelium.

Secondly, the stainable colloid approaches nearest the normal type in the true colloid glands and gradually becomes paler, more vacuolated and granular as we pass through the transitional forms to the true active marked hyperplasias, where it is generally absent or nearly so.

Thirdly, the vascularity and condition of the vessels show distinct and graded changes from the comparatively very slightly vascular pure colloid glands up to the markedly vascular active hyperplasias, while the vessel walls in pure colloid glands show distinct obliterating endarteritis similar, histologically, to that occurring in the involuting uterus or thymus.

These gradations of anatomical changes in the epithelium, the colloid and the vessels are very striking in the dog where such a series of colloid glands is easily obtained (in goitrous districts).

2. AGE OF THE ANIMALS.

The factor of age is important. Our only series of thyroids in which sufficiently large numbers of naturally occurring colloid glands were found (dog and man) illustrate very strikingly that colloid glands occur in older animals while the active hyperplasias occur in younger animals. This has long been recognized however, and is implied in the commonly used term "colloid degeneration of" which also implies the existence of an earlier and different anatomical condition of the gland. This factor of age differences between colloid and hyperplastic glands is in itself evidence that, normally, colloid glands are derived from hyperplasias; but above all

else it raises the question of whether this colloid change might [132] not be interpreted as physiological as well as pathological.

In this connection some of our earlier experiments, undertaken to repeat Halsted's¹ work on compensatory hypertrophy of the thyroid, might be of value.

3. CHANGES FOLLOWING THE REMOVAL OF ONE LOBE.

As most of our dogs when admitted to the laboratory show some degree of active hyperplasia of the thyroid it occurred to us to remove but one lobe from each of a few animals and note what occurred.¹ All the lobes removed showed some degree [133] of hyperplasia. The dogs were kept from 24 days to one year, and on examining the remaining lobe we found, instead of further hyperplasia in all, as expected, that in some cases the remaining lobe had reverted to the colloid state while in others the remaining lobe had undergone further hyperplasia.

These observations are presented in the following tables:

TABLE Ia.

No. of dog; sex; age; weight.	Date of first operation.	Date of second operation.	Lobe removed; weight of (gm.)	Histological classification of lobe.	Iodin per gram dried.	Iodin per gram fresh.
D-99a. male, middle, 8.4 kg.	29-I-06		Rt.; 7.2	Early gland. hyperplasia.	Not det	term'd.
D-99b.		16-I-07	Lt.; 4.5	Colloid.	1.538	0.458
D-85a. male, middle, 15.9 kg.	17-I-06		Rt.; 5	Early gland. hyperplasia.	Not det	term'd.
D-85b.		11-I-07	Lt.; 3.85	Colloid.	2.784	0.812
D-130a. female, middle, 9.6 kg.	14-II-06		Rt.; 1.9	Mod. gland. hyperplasia.	Not det	term'd.
D-130b.		30-X-06	Lt.; 1.5	Early gland. hyperplasia.	"	"
D-131a. male, middle, 9.7 kg.	14-II-06		Rt.; 6.9	Mod. gland. hyperplasia.	"	"
D-131b.		27-V-06	Lt.; 6	Mod. gland. hyperplasia.	"	"
D-207a. m. middle, 5.4 kg.	6-X0II-		Rt.; 2.1	Mark'd gland. hyperplasia.	"	"
D-207b.		27-I-07	Lt.; 1.6	Colloid-early gland. hyperplasia.	"	"

¹ Johns Hopkins Hosp. Rep., Balto., 1896, I, 373.

TABLE Ib.

[133] No. of dog; sex; age; weight.	Date of first operation.	Date of second operation.	Lobe removed; weight of (gm.)	Histological classification of lobe.	Iodin per gram dried.	Iodin per gram fresh.
D-100a, male, middle, 11.81 kg.	29-I-06		Rt.; 2.4	Mod. gland. hyperplasia.	Not de	term'd.
D-100b.		9-I-07	Lt.; 1.9	Mark'd gland. hyperplasia.	0.171	0.045
D-175a, male, puppy, 8.4 kg.	25-IV-06		Rt.; 1	Mod. gland. hyperplasia.	Not de	term'd.
D-175b, 13.2.		25-I-07	Lt.; 1.05	Mark'd gland. hyperplasia.	0.135	0.029
D-208a, male, middle.	11-XII-06		Rt.; 3	Mod. gland. hyperplasia.	Not de	term'd.
D-208b.		4-I-07	Lt.; 3.5	Mark'd gland. hyperplasia.	"	"

Table Ia includes those cases in which reversion occurred in the remaining lobe, and Table Ib those cases in which further hyperplasia occurred. All these animals were kept in the same kennel, subjected to the same conditions, and clinically were in excellent health at the time of killing.

At first glance these observations seemed to us only a confirmation of the well known fact brought out by Halsted, viz: That if sufficient gland is not removed there is no compensatory hyperplasia of the remaining portion. However, on closer study there seemed to be more than this. In one group there was a reversion to a more normal type of gland while in the other there was further hyperplasia. All showed slight active hyperplasia of the first lobe removed, but the individual differences were slight. All were kept under similar conditions as far as possible. There were not sufficient differences in the size of the glands of the two groups or of the age of the animals to be of noteworthy importance, and we were forced to conclude that other factors than the amount of thyroid were concerned, not only in those cases where reversion occurred but also in those in which further hyperplasia resulted. Here are seen opposite histologic changes under apparently constant conditions. Is one pathological and the other physiological? We are inclined to look upon both as physiological in the sense that they represent the result of nature's attempts at establishing a normal condition. On this basis those cases which showed further hyperplasia easily

become physiological (compensatory hyperplasia), but those [133] cases which showed a colloid change (reversion) cannot be interpreted as physiological unless we suppose the existence of another factor than quantity of thyroid—some substance normally needed by the animal and whose presence or absence also has an influence on the cellular activities of the gland.

4. THYROID HYPERPLASIA AND REVERSION.

In the light of this possibility that other factors than quantity of gland determine whether a gland already actively hyperplastic is to revert to the colloid state or undergo further hyperplasia the following observation is important: In the past two years we have from time to time removed small pieces of thyroid for histologic examination and then kept the animals for further experiments as needed. Looking over our records we find eight such cases. All were goitrous dogs and kept under the same conditions. Histologically the pieces of thyroids removed showed degrees of hyperplasia ranging from "marked" to "early-moderate." At the second operation, ranging from twenty days to three months later, it was found that the thyroids in all eight had undergone histologic changes toward colloid glands, *i. e.*, reversion—some only slightly, while others showed the completed changes to colloid. The dogs were all kept under the same laboratory conditions and liberally fed on cooked meat and bread. The problem is why these dogs, during their street life, maintained progressive hyperplasias while during their laboratory careers their thyroids, without exception, tended to revert to colloid glands. Certainly one thing seemed established, that some factor still unknown was influencing these gland changes, and from the clinical standpoint favorably, since the animals all gained weight.

5. EFFECT OF ADMINISTRATION OF IODIN, ETC.

It was at this stage that we began to study experimentally the effects of iodine on the thyroid, thinking that further insight might be had by very careful comparisons of the histological structure with the iodine content. At any rate the question of iodine as a factor in these changes must either be

[133] more definitely established or eliminated, since clinically it has long been recognized as a specific remedy in the disease, and the work of Baumann, Oswald, Roos, Weiss, Hunt and others has established not only its normal presence in the [134] thyroid but that it is of the greatest significance in the physiological activity of the thyroid substance. Our earlier experiments with feeding iodine have shown that coincident with the administration of iodine to dogs with active thyroid hyperplasias there occurs a return to the colloid state which histologically is identical with the spontaneously occurring colloid gland. This change in the dog is complete in from 20 to 30 days if small doses of some iodine-containing compound (0.5 cc. syr. ferrous iodid) are administered daily during the period. Since then we have undertaken experiments for tracing this process step by step during the administration of iodine. Thus we have removed every 5-7 days a piece of the gland sufficient for histological control and iodine determination with invariably the following result: That as the gland histologically changed to the colloid state there was a corresponding rise in the iodine content. A typical case may be reported in full.

CASE A-119.—Male, black mongrel, aged 8 months, admitted April 6, 1908. General nutrition good, weight 8 kg. Thyroid lobes are symmetrically enlarged and appear about the size of hen's eggs. They are soft, compressible, with a definite expansile pulsation and a palpable thrill. There is a palpable isthmus.

April 10, 1908. Under ether anaesthesia a portion of the left lobe was removed, weighing 9.825 gm.

There was slight hæmorrhage. Moderate distension of the lymphatic trunks coursing over the gland. Operation lasted one hour. Dog made excellent recovery.

Gross Description of Portion of Gland Removed.—The capsule is slightly thickened, gland tissue soft, grey-red, very vascular, and no visible colloid.

Histological Diagnosis.—Marked glandular hyperplasia.

Iodine per gm. dry = 0.200 mgm.
 " " " fresh = 0.040 "

April 10, '08,	gave	10	gtt.	syr. fer. iodid	by	mouth.
" 11, "	"	30	"	"	"	"
" 12, "	"	40	"	"	"	"
" 14, "	"	40	"	"	"	"

April 15, under ether anæsthesia, the remaining portion of [134] the left lobe was removed, weight 20.5 gm. The dog withstood operation well.

Gross Description of the Portion Removed.—Similar to first portion as described above except that there is some visible colloid and the consistency is somewhat firmer.

Histological Diagnosis.—Colloid—moderate glandular hyperplasia.

Iodin per gm. dry = 2.861 mgm.

“ “ “ fresh = 0.553 “

April 16. Dog in excellent condition, 40 gtt. syr. fer. iodid per mouth.

April 18. 100 gtt. syr. fer. iodid.

April 19. 100 gtt. syr. fer. iodid.

April 21. Bandages removed together with stitches. Healing per primam, 60 gtt. syr. fer. iodid.

April 22. Under ether anæsthesia a portion of the right lobe, weighing 1.5 gm., was removed. Immediately upon exposure of the gland it was noticeably different from the gland of previous operations in that it was much less vascular, firmer and translucent.

Gross Description of Portion Removed.—Capsule slightly thickened. Colloid is visible. Consistency moderately firm. Color is reddish-translucent.

Histological Diagnosis.—Colloid—moderate glandular hyperplasia.

Iodin per gm. dry = 4.078 mgm.

“ “ “ fresh = 0.860 “

April 23. Dog in good condition. (From this time on no iodine was administered.)

April 24. No sign of infection, eats heartily.

April 26. Wound clean, healed.

April 28. Under ether anæsthesia a portion of the right lobe weighing 7.2 gm. was removed. Dog withstood operation well, no hæmorrhage. The remaining portion of the gland has notably decreased in size.

Gross Description of the Portion Removed.—Gland is firm, colloid abundant, capsule moderately thickened, vascularity noticeably lessened.

Histological Diagnosis.—Colloid—early glandular hyperplasia.

Iodin per gm. dry = 3.353 mgm.

“ “ “ fresh = 0.749 “

April 30. Slight œdema of jaw; otherwise in good condition.

[134] May 3. Slight diarrhœa, wound healed and bandage removed.

May 6. Under ether anæsthesia a portion of the remaining part of the right lobe, weighing 6.5 gm., was removed. Rapid recovery from operation.

Gross Description of Portion Removed.—The gland tissue is hard, clear, yellow in color, colloid abundant, very viscid, vascularity normal.

Histological Diagnosis.—Pure colloid gland (goitre).

Iodin per gm. dry = 3.522 mgm.

“ “ “ fresh = 0.894 “

May 8. No swelling of jaw, no evidence of tetany; apparently both vocal cords paralyzed.

May 11. Wound healed per primam. Dog active, appetite excellent.

May 27. Condition excellent, fat, hair glossy.

June 1. Under ether anæsthesia a hurried examination failed to find the remaining part of right lobe, wound closed.

June 4. Stitches removed, wound healed.

June 15. Under ether anæsthesia the remaining portion of right lobe was found and part removed. After the operation had been completed the dog was killed by the careless administration of ether. An autopsy was immediately performed and the remainder of the right lobe, weighing 0.550 gm., was removed. There were two large accessory aortic thyroids, together weighing 0.750 gm. Their gross characteristics are the same as the portion of the thyroid lobe proper. Spleen and thymus slightly enlarged. Otherwise all the other organs were perfectly normal, both gross and microscopically. Weight of dog, 11.9 kg.

Gross Description of Thyroid Removed at Autopsy.—Colloid abundant, color clear yellow, firm to the touch, and of normal vascularity.

Histological Diagnosis.—Pure colloid gland (goitre).

Iodin per gm. dry = 2.770 mgm.

“ “ “ fresh = 0.554 “

Summary.—The dog was under observation from April 6, 1908, to June 15, 1908—70 days, during which time six operations were performed consisting of the successive removals of portions of the thyroid and accompanied by the administration of moderate doses of syr. fer. iod. for a period of 12 days following the first operation. After this the dog got no iodine except what might have been obtained from a liberal diet consisting of cooked meat, bread, water and milk. Ar-

ranging the iodine contents and histological diagnoses of the [135] portions of thyroid in the order of their removal, we have:

Histological Diagnosis.		Iodine per gm.	
		fresh, mgm.	dried, mgm.
1st operation.	Marked glandular hyperplasia	0.040	0.200
2d	“ Colloid—moderate-marked ..	0.553	2.861
3d	“ Colloid—moderate	0.860	4.078
4th	“ Colloid—early	0.749	3.353
5th	“ Pure colloid	0.894	3.522
6th	“ Pure colloid	0.554	2.770

This case illustrates the rapidity with which iodine is taken up by the hyperplastic thyroid and the rapidity of the process of reversion as well. The dog grew rapidly, gaining in the 70 days 4.9 kg.

As the histologic appearances of the spontaneously occurring colloid glands are identical with those artificially produced by administration of iodine, and since the histologic characteristics of colloid glands so closely resemble those of the normal glands, it becomes of interest to compare the iodine contents of normal and of spontaneously produced colloid glands. It suffices here to state that such comparisons have been made, and they show that the iodine contents of these two groups are practically parallel, and that the iodine contents of colloids are also the nearest approach to those of normal glands with which one meets. Indeed they may equal those of normal glands.

Thus far we have considered anatomical and chemical characteristics of colloid glands, both those artificially produced and the spontaneously occurring ones, and have compared the findings with those of normal glands. In a sentence, it was found that colloid glands, both as regards their histological characteristics and iodine contents, were the nearest approach to the normal gland that is possible for actively hyperplastic thyroids.

6. COMPARISON OF BIOLOGICAL REACTIONS OF COLLOID AND NORMAL GLANDS.

Next in order, we undertook studies of the *biological characteristics* of colloid glands as compared with those known

[135] to be true of normal glands. First, we took colloid glands, and from time to time removed parts in the attempt to produce compensatory hyperplasia of the remaining part, just as occurs in the similar treatment of normal glands. The following case is illustrative:

CASE A-106.—Middle-aged female, white, bull-terrier. Admitted June 1, 1907, in excellent condition, weight 11.8 kg. Physical examination revealed symmetrical enlargement of both thyroid lobes, each lobe roughly measuring 5x3.5 cm. Definite isthmus palpable. Lobes firm, hard and quite freely movable. Clinical diagnosis of pure colloid goitre was made on basis of excellent general condition and the firm, hard, non-pulsating lobes of thyroid.

June 5, 1907. Under ether anæsthesia right lobe was removed, weight 29.5 gm.

Gross Description.—Capsule 1 mm. thick, of dense white fibrous tissue. Gland tissue on section is clear brownish-yellow (old hæmorrhages), with abundant colloid, white fibrous trabeculæ are prominent throughout. Specimen saved for iodine determination and histological examination.

Histological Diagnosis.—Pure colloid gland (goitre).

Iodine per gm. dry = 0.308 mgm.

“ “ “ fresh = 0.033 “

June 18, 1907. Wound healed per primam, bandage removed, dog in excellent condition, appetite good.

July 15, 1907. Under ether anæsthesia about one-half of the remaining left lobe was removed, weight 15 gm.

Gross Description of Part Removed.—Capsule thick, color and colloid much the same as the previous portion of the gland.

Histological Diagnosis.—Pure colloid gland (goitre).

Iodine per gm. dry = 0.554 mgm.

“ “ “ fresh = 0.066 “

August 15, 1907. Dog in fair condition, wound healed, weight 9.52 kg.

September 10, 1907. Under ether anæsthesia about one-half of remaining half of left lobe removed, weight 3 gm. Specimen saved for iodine and histological examination.

Gross Description.—Quite vascular, bright red, moderately firm, some visibly dilated lymphatic trunks, some visible colloid.

Histological Diagnosis.—Colloid—moderate glandular hyperplasia.

Iodine per gm. dry = 0.554 mgm.

“ “ “ fresh = 0.099 “

September 20, 1907. Dog in fair condition, wound healed. [135]

December 7, 1907. Under ether anæsthesia remaining portion of left lobe was removed (as nearly as possible, since fibrous adhesions made it practically impossible to remove all traces of lobe).

Gross Description of Portion Removed.—Weight 4.5 gm., color bright red, soft, visible fibrous trabeculæ, capsule much thickened, quite vascular, some visible colloid.

Histological Diagnosis.—Marked glandular hyperplasia.

Iodin per gm. dry = 0.115 mgm.

“ “ “ fresh = 0.022 “

December 11, 1907. Dog has ravenous appetite. On removing bandage slight skin infection noted, washed with HgCl₂ and dressed.

December 22, 1907. Wound healed. Dog still has ravenous appetite; given sulphur bath on account of beginning mange.

January 4, 1908. Dog very weak, emaciated, weight 9.1 kg., slight diarrhœa, with visible cardiac impulse that shook the dog. Dog has showed no signs of tetany. As the dog was rapidly becoming weaker, in spite of its good appetite, it was decided to administer small doses of iodine in the form of syr. fer. iod.; beginning January 4, 10 gtt. daily was given. At first the dog seemed to improve, and between January 4 and 18 gained 2.3 kg.

January 21, 1908. Dog died suddenly this afternoon; was not seen at time of death. Autopsy (probably one hour after death) showed that the increased weight was due to œdema of the fatty tissues. Both thyroid lobes were absent. The heart was enlarged and dilated, especially the right side. Pulmonary congestion and œdema. Stomach, liver, kidneys, brain and pituitary body normal in their gross appearances. There was quite a large mass of thymus tissue in the sub-sternal fat, and also two accessory thyroids. These two accessory thyroids weighed 0.95 gm. In their gross appearance they were soft, greyish-red and vascular.

Histological examination of the accessory thyroids showed a moderate glandular hyperplasia.

Iodin per gm. dry = 0.410 mgm.

“ “ “ fresh = 0.095 “

A histological examination and iodine determination were made [136] on the thymus gland with the following result:

Histological examination revealed the presence of numerous duct-like spaces lined by columnar epithelium, and containing desquamated epithelial cells and a pink staining albuminous material (a condition common to about 20 per cent of the dogs

[136] in this locality). One accessory parathyroid was found in the thymus upon histological examination.

Iodin per gm. dry = 0.018 mgm.
" " " fresh = 0.006 "

Summary.—Dog was under observation from June 1, 1906, to January 21, 1907, practically seven months. During this time parts of the thyroid were removed on four different occasions. The first and second specimens were histologically pure colloid, while the third and fourth specimens removed showed, respectively, colloid with moderate, and colloid with marked glandular hyperplasia.

The iodine determinations of these four specimens showed, roughly, a decrease in the iodine content, proportional to the degree of hyperplasia. The accessory thyroids, removed post-mortem, while showing histologically a moderate glandular hyperplasia, showed a noticeable increase in their iodine contents over the last operative specimen. This was probably due, as was also the presence of iodine in the thymus, to the feeding of iodine during the last two weeks of life. The presence of iodine in the thymus was not due to the presence of accessory thyroids, a possibility suggested by Cunningham and Mendel (*Am. J. Physiol.*, 1900, III, 285). The noteworthy increase in body-weight during the last three weeks might be interpreted as of myxœdematous origin, although there is no positive anatomical basis for such an opinion, even though both thyroid lobes had been removed.

In this case it is clearly seen that a compensatory change occurred following partial excision. The change is identical with that which occurs in the normal gland, and has been admirably described by Halsted, *i. e.*, the flattened cubical cells lining the enlarged alveoli increase in size, first cubical, then low columnar, then high columnar, together with a lessening and finally a disappearance of the stainable colloid, and at the same time a marked increase in vascularity. The change is as a rule not quite uniform as some alveoli contain densely staining colloid and flattened epithelium, while all the surrounding alveoli have undergone true hypertrophy.

Thus it seems highly probable that colloid glands react like normal glands in the experiments of their partial removal.

7. PREVENTIVE EFFECT OF IODIN IN SECONDARY HYPERPLASIA.

Continuing along this line of biological experiments, it is^[136] known that the administration of iodine will prevent the occurrence of compensatory hyperplasia following partial excision in normal glands which otherwise would hypertrophy. The following cases are illustrative of what occurs in the normal glands.

CASE A-26.—Female puppy, age three months, admitted February 10, 1907, weight 2.4 kg., in fair condition, no palpable thyroids.

February 15, 1907. Under ether anaesthesia, right lobe removed, weight 0.24 gm.

Gross Description.—Capsule thin, delicate, color reddish-translucent, visible colloid normal, firm consistency.

Histological Diagnosis.—Normal thyroid.

Iodin per gm. dry = 2.300 mgm.
“ “ “ fresh = 0.380 “

February 19, 1907. Dog in excellent condition, wound healed, bandage removed, weight 2.4 kg.

February 21, 1907. Beginning to-day 1 gtt. saturated alcoholic solution of iodine was daily administered with its ration, for 15 days, ending March 8, 1907. From this date on no iodine was given.

March 20, 1907. Dog growing rapidly, clinically in excellent condition.

April 2, 1907. Killed with chloroform this morning, weight 4 kg.

At autopsy remaining lobe (right) weighed 0.305 gm., color clear, reddish-yellow, colloid abundant, gland tissue firm, capsule thin and delicate.

Histological Diagnosis.—Normal thyroid.

Iodin per gm. dry = 3.467 mgm.
“ “ “ fresh = 0.705 “

The fat deposits were normal. Spleen, kidneys, liver, lungs, heart and brain were normal in gross appearance.

CASE T-25.—Female pup, aged 112 days, weight 1.8 kg., excellent condition (reared in laboratory).

September 6, 1907. Operated upon and the left lobe removed. Weight 0.350 gm. Normal in gross appearance, and also upon microscopic examination. No iodine determination.

September 11. Wound healed, bandage removed.

[136] October 30. Weight 2.6 kg., excellent condition, killed by another dog. Right lobe removed and at autopsy weighed 0.355 gm.

Gross Appearance.—Soft, vascular.

Microscopic Diagnosis.—Moderate glandular hyperplasia. No iodine determination.

This case (T-25) illustrates what usually occurs in young dogs with normal glands following the removal of one lobe, viz: compensatory hyperplasia of the remaining lobe; and Case A-26 shows that this compensatory hyperplasia may be prevented by the administration of iodine although the thyroid increases in size in proportion to body weight. These cases, with many other similar experiments, also suggest that hyperplasia accompanied by a disappearance of the colloid and a change to columnar epithelium is not a part of the normal growth of a normal gland.

While we have no separate experiments on colloid glands to parallel the above cases, there have occurred several cases which indicate the same to be true for colloids, viz: That in the presence of full amounts of iodine smaller amounts of colloid gland suffice to supply the animal's needs. This being true it is obvious that by withholding iodine the hypertrophic changes may be hastened. At first a diet as free from iodine as possible was considered, and indeed attempted, but it is fraught with so many difficulties (well stated by Dochez, Johns Hopkins Hospital Bulletin, 1908, XIX, 235), chief among which is that we may be depriving the animal of other substances necessary to its normal economy in the attempt to eliminate iodine, that we chose merely to use a raw meat diet (beef). As will be brought out more fully in a later publication the restricting of iodine does hasten the occurrence of hypertrophy both in normal and in colloid glands.

The following case, since it combines several of the points just mentioned, may be reported in full:

CASE A-121.—Male, middle-aged fox-terrier, good condition, weight 7.3 kg. Admitted April 20, 1908. Thyroid lobes are symmetrically enlarged, joined by a palpable isthmus and roughly measuring 5x2.5 cm. The consistency is moderately firm; there is a definite, though slight, expansile pulsation; no thrill.

April 22, 1908. Under ether anaesthesia a part of the right lobe, weighing 4.6 gm., was removed. Dog withstood operation well.

Gross Description of Specimen Removed.—The capsule is somewhat thickened; vessels distinctly enlarged, color yellowish-opaque, consistency moderately firm and colloid is barely visible, as are the whitish ring-like outlines of the enlarged alveoli.

Histological Diagnosis.—Colloid—moderate glandular hyperplasia.

Iodin per gm. dry = 0.269 mgm.

“ “ “ fresh = 0.059 “

April 24, 1908. Dog is in excellent condition.

April 26, 1908. Bandage removed, no evidence of infection. Dog does not seem quite normal, appetite poor.

April 28. Under ether anæsthesia another portion of the right lobe, weighing 7.6 gm., was removed. Excellent recovery.

Gross Description.—Same as first specimen.

Histological Diagnosis.—Colloid—moderate glandular hyperplasia.

Iodin per gm. dry = 0.455 mgm.

“ “ “ fresh = 0.099 “

April 30, 1908. Slight œdema of jaw, appetite good.

May 8, 1908. Wound healed, dog in perfect health.

May 9, 1908. Under ether anæsthesia the remaining portion of the right lobe was removed, weighing 6.4 gm. Excellent recovery.

Gross Description.—Gland much firmer than previous specimens, has a distinct yellowish translucent appearance and more visible colloid, vascularity still above normal. The enlarged alveoli are more distinct.

Histological Diagnosis.—Colloid—early moderate glandular hyperplasia.

Iodin per gm. dry = 0.692 mgm.

“ “ “ fresh = 0.167 “

May 11, 1908. Wound in good condition, dog has good appetite.

May 20, 1908. Wound perfectly healed.

May 21, 1908. Under ether anæsthesia a portion of the left lobe, weighing 3.6 gm., was removed. Dog made excellent recovery.

Gross Description.—There are scattered areas of brown pigmentation (old hæmorrhage), colloid normal, vascularity still slightly above normal. The enlarged alveoli are more distinct.

Histological Diagnosis.—Colloid—early glandular hyperplasia.

Iodin per gm. dry = 1.838 mgm.

“ “ “ fresh = 0.520 “

[137] May 27, 1908. Dog in excellent condition, wound healed.

June 2, 1908. Under ether anæsthesia another portion of the left lobe, weighing 1.2 gm., was removed. Large quantities of ether had to be used, and there was excessive bronchial secretion, otherwise the dog withstood the operation well.

Gross Description.—Colloid abundant, color clear, yellow, translucent, tissue firm, vascularity normal.

Histological Diagnosis.—Colloid—early glandular hyperplasia.

Iodin per gm. dry = 1.774 mgm.

“ “ “ fresh = 0.446 “

June 3. Dog in good condition.

June 8. Bandage had slipped and dog had scratched skin wound open, wound granulating, no pus.

June 12. Wound healed. Under ether anæsthesia another portion, weighing 4.85 gm., was removed. Dog made excellent recovery. Large quantities of ether necessary.

Gross Description.—Colloid abundant, yellow, translucent in color, tissue firm, normal vascularity.

Histological Diagnosis.—Colloid—early glandular hyperplasia.

Iodin per gm. dry = 1.427 mgm.

“ “ “ fresh = 0.369 “

June 16. Wound healed, stitches removed, dog in excellent condition.

June 27. Under ether anæsthesia removed another portion of the left lobe, weighing 4.2 gm. Dog made good recovery, some difficulty was encountered with mucus.

Gross Description.—Colloid abundant, color translucent yellow, tissue firm, vascularity normal. Outline of enlarged alveoli distinct.

Histological Diagnosis.—Pure colloid gland (goitre).

Iodin per gm. dry = 2.170 mgm.

“ “ “ fresh = 0.550 “

July 2. Stitches removed, wound healed.

July 3. Mange suspected on account of some cutaneous irritation. An ointment of sulphur and lard was applied.

July 10. Dog in excellent condition. Under ether anæsthesia another portion of the left lobe, weighing 2 gm., was removed. Dog made excellent recovery from operation.

Gross Description.—Gland similar to last specimen described.

Histological Diagnosis.—Colloid—early glandular hyperplasia.

Iodin per gm. dry = 1.091 mgm.

“ “ “ fresh = 0.188 “

July 11. A prophylactic dose of 1 cc. of a 5 per cent solution [137] of calcium chloride was given with food, although there was no evidence of tetany.

July 14. Calcium chloride stopped. Dog in excellent condition.

July 18. Wound healed. Dog in excellent condition.

September 1. Dog in excellent condition, has gained in weight, now weighs 9.5 kg.

September 13. Under ether anæsthesia another portion of the left lobe was removed, weight 0.5 gm. Aside from large amount of ether necessary, and excessive bronchial secretion, dog withstood operation well.

Gross Diagnosis.—Tissue more vascular than in previous specimen, visible colloid distinctly less. The cut surface shows fine greyish trabeculæ, giving the specimen a distinct opacity.

Histological Diagnosis.—Colloid—early glandular hyperplasia.

Iodin per gm. dry = 1.082 mgm.

“ “ “ fresh = 0.206 “

September 15. Dog in excellent condition; used sulphur ointment again.

September 19. Wound healed, stitches removed.

October 3. Dog apparently normal, given 20 gtt. syr. fer. iod. by mouth.

October 25. Finished the course of 15 cc. syr. fer. iod. by mouth.

November 1. Under ether anæsthesia a part of the remaining portion of the left lobe was removed, weighing 0.8 gm. The scar tissue was moderately dense about it, but no difficulty was [138] met with and dog rallied quickly from operation.

Gross Description of Specimen Removed.—Scar tissue at one edge is quite vascular, color of gland is clear, reddish-translucent, consistency firm, colloid normal. The alveoli are distinct.

Histological Diagnosis.—Pure colloid gland (goitre).

Iodin per gm. dry = 1.925 mgm.

“ “ “ fresh = 0.513 “

November 2. As the operation injury to the tissue approached very near to the upper pole, and hence there was danger of having injured the presumably only remaining parathyroid, it was deemed advisable to give 10 cc. of a 5 per cent solution of calcium chloride as a prophylaxis.

November 4. 10 cc. of calcium chloride given; no evidence of tetany.

November 5. Wound healed. Stitches removed.

November 17. Dog very fat, weight 12.1 kg., active and alert.

December 21. Dog in excellent condition.

[138] December 22. Under ether anæsthesia a part of the remaining portion of the left lobe was removed, weighing 0.355 gm.

Gross Description.—Color brownish-red, colloid visible, though reduced, vascular.

Histological Diagnosis.—Colloid—early glandular hyperplasia.

Iodin per gm. dry = 1.540 mgm.

“ “ “ fresh = 0.305 “

December 26. Wound healed, stitches and bandage removed. Calcium chloride stopped. Weight, 12 kg.

In this case at the time of admission the thyroid was classified as colloid—moderate glandular hyperplasia, in which the histological picture was that of a spontaneous slow reversion from an active hyperplasia rather than that of a colloid gland undergoing further hyperplasia. We have summarized the experiment in the following tabulation:

SUMMARY.

Date of Operation.	Histological Diagnosis.	Iodin per gm.	
		dry, mgm.	fresh, mgm.
April 22, '08.	Colloid—moderate glandular hyperplasia	0.269	0.059
April 28, '08.	Colloid—moderate glandular hyperplasia	0.455	0.099
May 9, '08.	Colloid—early glandular hyperplasia	0.692	0.167
May 21, '08.	Colloid—early glandular hyperplasia	1.838	0.520
June 2, '08.	Colloid—early glandular hyperplasia	1.774	0.446
June 12, '08.	Colloid—early glandular hyperplasia	1.427	0.369
June 27, '08.	Pure colloid gland.....	2.170	0.550
July 10, '08.	Colloid—early glandular hyperplasia	1.091	0.188
Sept. 13, '08.	Colloid—early glandular hyperplasia	1.082	0.206
Nov. 1, '08.	Pure colloid gland.....	1.925	0.513
Dec. 22, '08.	Colloid—early glandular hyperplasia	1.540	0.305

Thus, in a single experiment, starting with active hyperplasia we have followed the process back to colloid; to hyperplasia again; back to colloid, and finally to hyperplasia for the second time.

8. SUMMARY AND DISCUSSION.

In the observations above recorded the following points^[138] were brought out:

(1) Colloid glands are in all their anatomical characteristics the nearest approach to normal glands that active hyperplasias can become.

(2) There are as many degrees and sizes of colloid glands as there are degrees and sizes of actively hyperplastic glands.

(3) There are all gradations from colloid glands to active hyperplasias.

(4) The iodine contents of colloid glands are the nearest approach to those of normal glands that it is possible for glands to attain to, which have once been the seats of active hyperplasia.

(5) Spontaneously occurring colloid glands are most frequently found in the well nourished and middle-aged animals.

(6) Colloid glands are known to occur from spontaneous reversion of hyperplasias or following the administration of iodine-containing substances to animals with hyperplasia, and in either case the resulting condition (colloid) is histologically the same.

(7) Partial removal of colloid glands is followed by the same compensatory hyperplasia as occurs in normal glands following their partial removal.

(8) The administration of iodine-containing substances will prevent the occurrence of secondary hyperplasia in colloid glands to the same extent that it prevents the occurrence of hyperplasia in normal glands following partial removal.

(9) It is possible by means of partial removals together with withholding and giving iodine to follow the process of reversion to a colloid gland; the process of compensatory hyperplasia, and the second process of secondary reversion in the same dog.

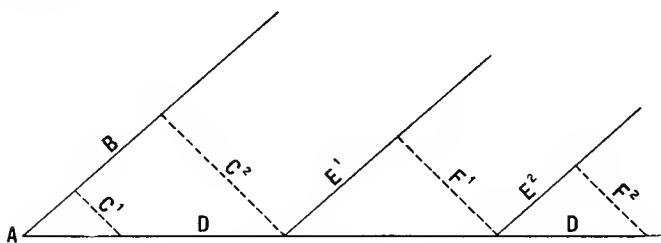
Thus it is seen that colloid glands as regards their *anatomical*, *chemical* and *general biological* characteristics obey all the laws of normal glands in so far as these laws are at present known.

These observations offer a rational explanation for the long

[138] known and ill understood phenomena of a goitre presenting some of the characteristics both of a colloid and of a hyperplasia (parenchymatous goitre) or of a hyperplasia occurring on a colloid basis, since it is possible to produce experimentally a hyperplasia on a colloid gland basis in just the same way as one produces a hyperplasia on a normal gland basis.

To illustrate the above fact from goitre in man, where such cases have been more frequently observed, this is what occurs in those cases recorded in the literature as "Secondary Graves' disease" or Graves' disease engrafted on an old colloid goitre in contrast with the so-called "Primary Graves' disease," which is the same process occurring on the basis of a normal gland. Then too the long life of man and a more careful study of goitre in man has allowed Lawson Tait (Edinb. M. J., 1875, XX, 993) to observe the "stair-step" like progress of goitre associated with multiple pregnancies. This process interpreted by our present standards would mean a hyper-
[139] plasia during the pregnancies with reversion to colloid gland during the intervals, with each succeeding reversion not returning to the size of the preceding reversion.

This relationship of hyperplasias to colloid glands and to normal glands may be best presented in the following diagram:



A, normal gland; B, all degrees of primary hyperplasia occurring on the basis of a normal gland; C-1, 2, the several degrees of hyperplasia returning to colloid state; D, colloid glands; E-1, 2, etc., the several degrees of secondary hyperplasia engrafted on the basis of a colloid gland; F-1, 2, etc., the secondary reversion of the secondary hyperplasias. Thus one might have tertiary hyperplasias and reversions, etc.

These data, *anatomical*, *chemical* and *biological*, we believe

are sufficient to justify the conclusion that in dogs and sheep, [139] at least, all pure colloid glands are reversions from degrees of active hyperplasia and are the nearest approach to the normal quiescent condition that glands can ever assume which have once undergone active hyperplasia. Further, this return to the colloid state is nature's evidence of a relief from some physiological deficiency. Lastly, the process of reversion being *physiological* rather than *pathological*, it seems to us to be more closely allied with the *involution type of atrophy* than with *degeneration*.

We are indebted to Profs. Stewart, Howard and Sollmann for their careful criticisms.

FURTHER OBSERVATIONS ON THE RELATION OF IODIN TO THE STRUCTURE OF THE THYROID GLAND IN THE SHEEP, DOG, HOG AND OX *

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INTRODUCTION

In this report we have collected our observations on the relation of the iodine content to the structure of the thyroid to include sheep, ox and hog thyroids. It is thus only a continuation of the work previously reported¹ concerning dogs' thyroids. The methods used and the anatomic classifications adopted are the same as those fully described in the above-mentioned article and elsewhere.²

COMPARISON OF THE IODINE CONTENTS OF SHEEP, DOG, HOG AND OX THYROIDS WITH THEIR RESPECTIVE ANATOMIC STRUCTURES

The following tables are compiled from iodine determinations made on the thyroids of 40 sheep, 67 dogs, 26 hogs and 37 oxen. As the basis of these tables we have used nine anatomic groups, viz.:

1. Normal glands.
2. Colloid glands (goiters).
3. Colloid-early glandular hyperplasia.
4. Normal-early glandular hyperplasia.
5. Early-glandular hyperplasia.
6. Early-moderate glandular hyperplasia.
7. Moderate glandular hyperplasia.
8. Moderate-marked glandular hyperplasia.
9. Marked glandular hyperplasia.

The normal and colloid groups are well defined, while the remaining seven groups are purely arbitrary divisions of the hyperplasias made for the purpose of facilitating analysis, since in reality one has to deal with a continuous gradation of hyperplastic changes occurring in either normal or colloid glands. In order to express this gradation, we have used the following terms: *normal-early glandular hyperplasia* to include

* From the Laboratories of Experimental Medicine and Pharmacology, Western Reserve University.

1. Marine (David) and Williams (W. W.): THE ARCHIVES INT. MED., 1908, i, 349.

2. Marine (David): The occurrence and physiological nature of glandular hyperplasia, etc. Johns Hopkins Hosp. Bull., 1907, xviii, 359.

those glands showing the very earliest hyperplastic changes occurring in normal glands; *colloid-early glandular hyperplasia* to include glands showing the earliest hyperplastic changes occurring in colloid glands, and the terms *early, moderate, marked*, etc., to include the other gradations up to and including the most extensive glandular hyperplasias met with.

In placing these glands in these several anatomic groups, we have compared all the glands of the four animals, the one with the other, in order that the same standard of classification might obtain in all.

In each of the following tables we have listed for comparison the iodine contents of sheep, dog, hog and ox thyroids having the same anatomic structure.

TABLE 1.—NORMAL GLANDS *

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep	19	4.614	2.288	2.467	1.318	0.694	0.686
		1.247			0.318		
		4.722			1.064		
Dog	3		3.205	3.322		0.757	0.777
		1.990			0.512		
		4.153			1.456		
Hog	18		2.412	2.515		0.778	0.884
		1.538			0.425		
		4.768			1.592		
Ox	17		3.254	3.461		1.069	1.117
		2.730			0.892		

* In each table E., M., A. are abbreviations for extreme, mean and average, respectively.

It will be seen that the upper extremes of iodine contents are fairly constant for all four animals, while the lower extremes show moderately wide variations, although the lowest of these lower extremes is always far in excess of the highest extremes of the succeeding group—normal-early glandular hyperplasias. This would indicate that there are considerable variations in the iodine contents within the group, even when no noteworthy anatomic changes are observed, although if individual comparisons of the iodine contents with the corresponding histologic preparations be made one can distinguish changes in the structure (too slight to warrant the introduction of a new group) corresponding to the variations in the iodine content; that is, glands with the highest iodine contents have a more flattened alveolar epithelium and *vice versa*, although all these glands appear in the table as normal.

The average iodine contents for the four animals show a surprising constancy and parallelism, viz.: 2.467 mg. for the sheep, 2.515 for the hog, 3.322 for the dog and 3.461 for the ox per gm. of dried thyroid.

The ox thyroids in our series have distinctly higher iodine contents than either the dog, sheep or hog. To know whether this is normally true would be of value in determining what relation exists between the normal iodine content and the normal weight of the thyroid, since oxen appear to have less thyroid per kilogram of body weight than do the other animals mentioned. From the experimental side it has been definitely shown that the amount of iodine in the thyroid does to a great extent control the size of the gland.

TABLE 2.—COLLOID GLANDS

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep	3	3.691			1.027		
			3.529	2.996		0.974	0.818
		1.769			0.455		
Dog	8	3.608			1.039		
			1.816	1.985		0.406	0.459
		0.846			0.132		
Hog	2	2.768			0.805		
			2.353		0.681
		1.938			0.557		
Ox	0

Owing to the small number of cases included, it is not possible to speak very specifically. However, in all three animals in which colloids were observed the upper extremes of iodine content are fairly constant, while the lower extremes show moderate variations. This agrees with what was observed in the normal glands, and our explanation is the same. Another point worthy of note is that, while the iodine per gram of colloid gland is in general lower than that of normal glands, yet, as will be seen, they approach nearest to the normal iodine content so far as we have found and may be raised to an equal content with the normal glands.

TABLE 3.—COLLOID-EARLY GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep	4	1.000			0.282		
			0.853	0.792		0.201	0.206
		0.461			0.138		
Dog	4	1.443			0.302		
			0.953	0.945		0.221	0.217
		0.431			0.125		
Hog	0
Ox	0

Table 3 and Table 4 deal with the most important anatomic and chemical changes concerned with the production of goiter, in that they represent the first deviation or change from the normal-colloid or quiescent glands. *Colloid-early glandular hyperplasias* differ from *normal-early glandular hyperplasias* in that the former are *secondary*³ hyperplasias, while the latter are *primary*. It is to be regretted that more colloid-early glands were not obtainable (the probable reason for this will be pointed out later). The extremes show a fair constancy. In the sheep the highest extreme iodine content is below the lowest pure colloid extreme. In the case of the dog this is in general true, though there are exceptions which we are not able to explain. The existence of these exceptions suggests, however, that from the histology alone one is unable to say whether a given gland is undergoing further hyperplasia from a less marked hyperplasia or *vice versa*. The averages also are constant and in every instance show the great drop in the percentage of iodine from that of pure colloid glands. This drop is, as will be seen in Table 4, identical with that occurring between the normal and normal-early glandular hyperplasia. Between no other groups are there comparable drops. This means that in both colloid and normal glands there are wide variations in the amount of iodine present, but that there is a quite constant lower limit of the iodine content necessary to maintain normal gland or pure colloid gland structure, and that this lower limit for colloids is slightly in excess of 0.217 mg. per gram of fresh thyroid for dogs and 0.206 mg. per gram of fresh gland for sheep, corresponding to 0.792 mg. and 0.945 mg. per gram of dried gland, respectively.

TABLE 4.—NORMAL-EARLY GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep	1	0.677	0.176
		1.296			0.318		
Dog	7	0.815	0.879		0.153	0.174	
		0.483			0.018		
Hog	1	1.230	0.337
		2.676			0.726		
Ox	7	2.307	2.317		0.653	0.628	
		2.000			0.482		

Table 4, together with Table 3, deals with the most important thyroid changes concerned in the production of goiter. It is seen that the highest extremes of iodine content are invariably below the lowest extreme

3. Secondary in the sense that this is the second time these glands have undergone active hyperplasia.

iodin contents of normal glands. This is even more evident with the means and averages. The table also shows that there is considerable difference between the average iodin content of sheep's thyroids and that of oxen thyroids, just as was seen to be true of the normal glands of these animals. It suggests, as was stated under Table 1, that oxen normally have more iodin and less thyroid per kilogram of body weight. In accordance with this, hyperplastic changes are manifest with an iodin content nearly four times that of the sheep's thyroids. But the most striking thing, just as in the colloid-early glands, is the great drop in iodin content from the normal, which must occur before hyperplastic changes are observed. The table shows that the lower limit of iodin necessary for the maintenance of normal structure is somewhat in excess of 0.176 mg. per gram of fresh gland for sheep, 0.174 for dogs, 0.337 for hogs and 0.628 for cattle, or 0.677, 0.879, 1.230, 2.317 mg. per gram of dried gland, respectively.

TABLE 5.—EARLY GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep.....	0
Dog	9	1.028			0.235		
		0.243	0.654	0.625	0.063	0.113	0.139
Hog	2	1.158			0.291		
		1.046	1.102	0.279	0.285
Ox	3	2.186			0.615		
		1.123	1.630	1.646	0.314	0.456	0.462

In the group of early glandular hyperplasia the iodin contents are still further lowered and the drop is practically the same in all four animals. The ox thyroids still show higher iodin contents than the other animals' glands for the same degree of thyroid hyperplasia as was also noted in the normal and normal-early glands.

TABLE 6.—EARLY-MODERATE GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep	1	0.548	0.131
Dog	1	0.262	0.082
		0.846			0.241		
Hog	3	0.769	0.769	0.795	0.198	0.233	0.224
		1.030			0.252		
Ox	5	1.000	1.000	1.000	0.222	0.226	
		0.969			0.205		

In the table of early-moderate glandular hyperplasia are collected those glands which histologically show a degree of epithelial proliferation (hyperplasia) too pronounced to be considered as early glandular hyperplasia and not sufficient to be classed as moderate glandular hyperplasia. As regards their iodine contents, the upper extremes are in every instance lower than the lower extremes of the preceding group (early glandular hyperplasia). So also the average iodine contents are about as much below those of the group of early glandular hyperplasias as the early glandular hyperplasias are below the group of normal-early glandular hyperplasias.

TABLE 7.—MODERATE GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep	1	0.400	0.091
		0.854			0.136		
Dog	9		0.345	0.368	0.076	0.078	
		0.101			0.026		
Hog	0
Ox	0

There being no glands from hogs or oxen and but one from the sheep series that histologically belonged to the group of moderate glandular hyperplasia, comparisons are impossible. The average iodine contents of the cases recorded are as usual below those of the preceding group.

TABLE 8.—MODERATE-MARKED GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep	5	0.092			0.014		
		0.000	0.024	0.031	0.000	0.003	0.004
		0.660			0.109		
Dog	9		0.231	0.283	0.042	0.055	
		0.058			0.011		
Hog	0
Ox	0

In the group of moderate-marked hyperplasia also there are but two animals represented. The extremes of iodine content in the dog thyroids are widely separated. As has already been pointed out, it is impossible to tell from the histology alone whether a given gland is undergoing further hyperplasia or is reverting to a lesser degree, in which latter event the iodine would be higher. Another factor must also be considered, that is, that dogs live under far less constant conditions than sheep and

oxen. It will be shown later that the more constant the conditions of life the more constant are the iodine contents. The averages show the same drop in the iodine contents proportional to the degree of increase of the hyperplasia.

TABLE 9.—MARKED GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodine per gm. dried.			Iodine per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep	6	0.036			0.006		
		0.000	0.000	0.006	0.000	0.000	0.001
					0.000		
Dog	18	0.640			0.123		
		0.008	0.073	0.114	0.002	0.014	0.023
Hog	0
Ox	5	0.270			0.062		
		0.077	0.215	0.189	0.016	0.042	0.041

Table 9 includes those glands having the most marked degree of thyroid hyperplasia and in consequence the lowest iodine contents. The only glands in which no estimable amount of iodine was found were in sheep, although, histologically, the degree of hyperplasia was no greater than in other glands which showed traces of iodine. The average iodine contents are all lower than the averages of the preceding group. So also the extremes are lower except in dogs' thyroids, in which the same wide variations are noted as in Table 8. Our explanation is the same.

SUMMARY AND DISCUSSION

Table 10, showing average iodine contents, has been introduced both as a summary and to emphasize the relation which exists between the iodine contents and the corresponding histologic structure.

TABLE 10.—AVERAGES

Anatomic Groups.	Sheep. Iodine per gm.		Dog. Iodine per gm.		Hog. Iodine per gm.		Ox. Iodine per gm.	
	Dried.	Fresh.	Dried.	Fresh.	Dried.	Fresh.	Dried.	Fresh.
Normal	2.467	0.686	3.322	0.777	2.515	0.884	3.461	1.117
Normal-early	0.677	0.176	0.879	0.174	1.230	0.337	2.317	0.628
Early			0.625	0.139	1.102	0.285	1.646	0.462
Early-moderate ..	0.548	0.131	0.262	0.082	0.795	0.224	1.000	0.226
Moderate	0.400	0.091	0.368	0.078
Moderate-marked.	0.031	0.004	0.283	0.055
Marked	0.006	0.001	0.114	0.023	0.189	0.041
Colloid	2.996	0.818	1.985	0.459	2.353	0.681
Colloid-early	0.792	0.206	0.945	0.217

Since colloid glands differ from normal glands essentially in that they have undergone active hyperplasia, two series (1), normal, and (2), colloid, must be recognized. Taking up the normal series, which is

practically complete in that it contains all the gradations of hyperplasia, it is seen that in all four species of animals the strictly normal glands have the highest iodine contents and those with marked glandular hyperplasia the lowest. The intervening groups show progressive decline, depending on the extent of the hyperplasia. The greatest drop in iodine content between any two successive groups occurs between the normal and the normal-early glandular hyperplasias, that is, those glands showing the earliest histologic deviation from normal. This great drop occurs with all four species and is similar in nature to the drop which occurs between the pure colloid glands and the colloid-early glandular hyperplasias. As has been said, this drop suggests that there is a minimum iodine content necessary for the maintenance of the normal or colloid state of the gland, and, since the amount of iodine present in normal or colloid glands is, as a rule, far in excess of this minimum, it is possible that this difference represents the reserve or factor of safety.

Certain details of this relation of iodine to the structure of the glands are more clearly shown in the full Tables 11, 12 and 13. Here it will be seen that by arranging the iodine contents in series from minimum to maximum, the glands are also arranged in series according to their histology, their colloid contents and their weights. In other words, the weights of the glands vary directly with the degree of hyperplasia and inversely with the percentage iodine content; the stainable colloid varies inversely with the degree of hyperplasia and directly with the iodine content, and the degree of hyperplasia varies inversely with the iodine contents (the normal and colloid series being, of course, considered separately).

It is also noticed that within any anatomic group there is considerable variation in the iodine contents. This is for the greater part due to the arbitrary anatomic groups, since the glands show histologic variations corresponding to the iodine variations, but not sufficient to warrant separate grouping. In other words, the arbitrary groups but imperfectly represent the gradations which the complete tables fully picture.

It may also be added that no special stress is laid on the actual figures of the iodine determinations, but only their relative importance as a series has been considered. Other observers with other methods may obtain different figures, but the relation between the iodine content and the gland structures, we believe, will always be found constant.

Passing now to the colloid series, it will be seen that only two groups of colloid glands have been observed: (1) pure colloids, (2) colloid-early glandular hyperplasia. This is noteworthy because in our human collection (to be reported), using the same anatomic classification and

TABLE 11.—PIGS' THYROIDS

Case No.	Age. Sex.	Condition.	Locality.	Weight of Gland.	Color.	Consistency.	Colloid.	Normal.	Colloid.	Normal-Early.	Colloid-Early.	Early.	Early-Moderate.	Moderate.	Moderate-Marked.	Marked.	Iodin per gm. Dried.	Iodin per gm.
P. 2.	10 mos. M. *	Good ..	Iowa.....	?	Fleshy red	Moderately soft.	Reduced.	+	0.769	0
P. 24.	10 mos. M.	"	"	?	"	Moderately soft.	"	+	0.769	0
P. 21.	10 mos. F.	"	"	?	"	Moderately soft.	"	+	0.846	0
P. 17.	10 mos. M.	"	"	?	Yellow-red, transluc..	Moderate....	Visible..	+	1.046	0
P. 7.	10 mos. F.	"	"	?	"	"	"	+	1.158	0
P. 16.	9 mos. F.	"	"	?	Clear yellow-red.....	Firm	"	+	1.230	0
P. 6.	10 mos. M.	"	"	?	"	"	Normal..	+	1.538	0
P. 18.	10 mos. M.	"	"	?	"	"	"	+	1.538	0
P. 5.	10 mos. F.	"	"	j	"	"	"	+	1.938	0
P. 19.	11 mos. M.	"	"	?	"	"	"	..	+	1.938	0
P. 25.	9 mos. F.	"	"	?	"	"	"	..	+	1.938	0
P. 12.	10 mos. F.	"	"	?	"	"	"	..	+	1.938	0
P. 20.	10 mos. M.	"	"	?	"	"	"	..	+	1.938	0
P. 4.	10 mos. F.	"	"	?	"	"	"	..	+984	0
P. 26.	10 mos. F.	"	"	?	"	"	"	..	+	1.997	0
P. 10.	10 mos. M.	"	"	?	"	"	"	..	+	2.307	0
P. 23.	8 mos. M.	"	"	?	"	"	"	..	+	2.517	0
P. 14.	8 mos. M.	"	"	?	"	"	"	..	+	2.615	1
P. 11.	8 mos. F.	"	"	?	"	"	"	..	+	2.768	0
P. 9.	8 mos. M.	"	"	?	"	"	"	..	+	2.768	0
P. 8.	2 yrs. F..	"	?	?	Pale yellow, transluc.	"	"	..	+	2.768	0
P. 1.	10 mos. M.	"	Iowa.....	?	Clear yellow-red.....	"	"	..	+	3.230	1
P. 15.	8 mos. M.	"	"	j	"	"	"	..	+	3.691	1
P. 3.	10 mos. M.	"	"	?	"	"	"	..	+	3.691	1
P. 22.	10 mos. F.	"	"	?	"	"	"	..	+	3.728	1
P. 13.	8 mos. F.	"	"	?	"	"	"	..	+	4.154	1

*Age estimated by butchers.

TABLE 12.—CATTLE THYROIDS

General.				Gross.				Microscopical.						Chem.		
Case No.	Age.	Sex.	Condition.	Locality.	Weight of Glands in gms.	Color.	Consistency.	Colloid.	Normal.	Colloid.	Normal-Early.	Colloid-Early.	Early-Moderate.	Moderate.	Moderate-Marked.	Iodin, per gm., Dried.
C. 34.	Young steer.*		Good..	Northern Ohio.	41	Opaque, pale brown.	Soft.	Absent	+ 0.077
C. 36.	"	"	"	Northern Ohio.	53	Very pale brown....	"	"	+ 0.154
C. 29.	Calf, fema e.		Poor..	Michigan..	370	" " "	"	"	+ 0.215
C. 30.	Young steer.		Good..	Northern Ohio.	39	" " "	"	"	+ 0.231
C. 35.	"	"	"	Northern Ohio.	13	Dark brown-red....	Moderate. ..	Visible	+ 0.270
C. 40.	"	"	"	Northern Ohio.	27	Brown red.....	"	"	+	0.969
C. 33.	"	"	"	Northern Ohio.	17	Dark brown-red....	"	"	+	0.969
C. 31.	"	"	"	Northern Ohio.	17	" " "	"	"	+	1.030
C. 37.	"	"	"	Northern Ohio.	16	Translucent, brown-red.	"	"	+	1.000
C. 38.	"	"	"	Northern Ohio.	19	Pale brown, translucent.	Firm	"	+	1.030
C. 39.	"	"	"	Northern Ohio.	16	Pale brown, translucent.	"	Normal..	+	1.123
C. 32.	"	"	"	Northern Ohio.	13	Brown red, translucent.	"	"	+	1.630
C. 65.	"	"	"	Northern Ohio.	12	Brown red, translucent.	"	"	+	2.153
C. 46.	"	"	"	Texas.....	12	Dark brown-red, translucent.	"	"	+	2.000
C. 51.	"	"	"	"	13	Pale brown-red, translucent.	"	"	+	2.186
C. 45.	"	"	"	"	13	Very pale yellow brown, translucent.	"	"	+	2.076
C. 48.	"	"	"	"	12	Pale yellow brown, translucent.	"	"	+	2.307
C. 64.	"	"	"	Northern Ohio.	13	Pale yellow brown, translucent.	"	"	+	2.615
C. 41.	Young bull..		"	Texas.....	11.5	Pale yellow brown, translucent.	"	"	+	2.676
C. 42.	Young steer.		"	"	12	Pale yellow brown, translucent.	"	"	+	2.384
C. 47.	"	"	"	"	11	Yellow-brown, translucent.	"	"	+	2.730
C. 44.	"	"	"	"	15	Pale brown, translucent.	"	"	+	2.922
C. 43.	"	"	"	"	11	Pale brown, translucent.	"	"	+	2.937
C. 49.	"	"	"	"	11	Pale brown, translucent.	"	"	+	3.107
C. 52.	"	"	"	"	12	Brown red, translucent.	"	"	+	3.091
C. 57.	"	"	"	"	12	Pale yellow, translucent.	"	"	+	3.254
C. 58.	"	"	"	"	11	Pale yellow, translucent.	"	"	+	3.537
C. 63.	"	"	"	"	11	Pale yellow, translucent.	"	"	+	3.230
C. 55.	"	"	"	"	12	Pale yellow, translucent.	"	"	+	3.230
C. 50.	"	"	"	"	14	Pale yellow, translucent.	"	"	+	3.384
C. 62.	"	"	"	"	12	Pale yellow, translucent.	"	"	+	3.630
C. 61.	"	"	"	"	12	Pale yellow, translucent.	"	"	+	3.630
C. 60.	"	"	"	"	11	Pale yellow, translucent.	"	"	+	3.230
C. 58.	"	"	"	"	12	Pale yellow, translucent.	"	"	+	3.999
C. 53.	"	"	"	"	13	Pale yellow, translucent.	"	"	+	3.999
C. 54.	"	"	"	"	11	Pale yellow, translucent.	"	"	+	4.153
C. 59.	"	"	"	"	11	Pale yellow, translucent.	"	"	+	4.768

*i.e. 3 to 5 yrs. as estimated by cattlemen.

†General term among cattlemen, meaning any part of Great Plains.

TABLE 13.—SHEEP THYROIDS

General.				Gross.				Microscopical.							Ch		
Case No.	Age. Sex.	Condition.	Locality.	Weight in grms.	Color.	Consistency.	Colloid.	Normal.	Colloid.	Normal-Early.	Colloid-Early.	Early.	Early-Moderate.	Moderate.	Moderate-Marked.	Marked.	Iodin, per gm.,
S. 33.	F 8 mos...	Good...	Seville, Ohio.	95.0	Gray red, translucent.	Soft.	Visible...									+	0.0
S. 37.	M. 10 mos	"	Seville, Ohio.	115.0	Gray red, opaque...	"	None									+	0.0
S. 39.	M. 9 mos...	"	Seville, Ohio.	85.0	" " "	"	"									+	0.0
S. 45.	M. 8 mos...	"	Seville, Ohio.	55.0	" " "	"	"									+	0.0
S. 20.	? 8 mos...	"	?	110.0	" " "	"	"									+	0.0
S. 36.	M. 9 mos...	"	Seville, Ohio.	120.0	Gray, translucent...	"	Visible...									+	0.0
S. 38.	M. 10 mos...	"	Seville, Ohio.	130.0	" " "	"	"									+	0.0
S. 34.	F. 9 mos...	"	Seville, Ohio.	98.0	" " "	"	"									+	0.0
S. 35.	F. 9 mos...	"	Seville, Ohio.	110.0	" " "	"	"									+	0.0
S. 59.	? 1 yr	"	?	6.0	Opaque, red, granular.	"	None...									+	0.0
S. 21.	M. 1 yr.	"	?	64.0	Opaque, red, granular.	"	Visible...									+	0.0
S. 49.	F. 8 mos...	"	?	48.0	Opaque, red, granular.	"	"									+	0.4
S. 47.	M. 9 mos...	"	?	6.0	Red-gray, translucent.	Moderate...	"									+	0.5
S. 32.	F. 4 yrs...	Fair...	?	370.0	Red-yellow, translucent.	Firm	Normal.				+						0.4
S. 43.	F. 5 yrs...	"	?	15.0	Red-yellow, translucent.	"	"				+						0.6
S. 51.	M. 9 mos...	Good...	?	18.0	Red-yellow, translucent.	"	Visible...					+					0.9
S. 50.	M. 9 mos...	"	?	16.0	Red-yellow, translucent.	"	"					+					0.7
S. 46.	F. 5 yrs...	Fair...	?	25.0	Clear yellow, translucent.	"	Normal,					+					1.0
S. 52.	? 1 yr.	Good...	?	5.9	Clear yellow, translucent.	"	"					+					1.2
S. 53.	? 1 yr.	"	?	6.7	Clear yellow, translucent.	"	"					+					1.2
S. 55.	? 1 yr.	"	?	6.5	Clear yellow, translucent.	"	"					+					1.4
S. 48.	F. 9 mos...	Fair...	?	5.9	Clear yellow, translucent.	"	"					+					1.6
S. 63.	F. 3 yrs...	Good...	?	8.0	Clear yellow, translucent.	"	"					+					1.6
S. 60a	M. 2 yrs...	"	?	58.0	Clear yellow, translucent.	"	"					+					1.7
S. 58.	? 1 yr.	"	?	4.5	Clear yellow, translucent.	"	"					+					1.8
S. 60.	F. 3 yrs...	Fair...	Northern Ohio.	8.0	Clear yellow, translucent.	"	"					+					2.1
S. 61.	F. 3 yrs...	"	Northern Ohio.	8.5	Clear yellow, translucent.	"	"					+					2.2
S. 62.	F. 4 yrs...	"	Northern Ohio.	8.0	Clear yellow, translucent.	"	"					+					2.2
S. 65.	F. 4 yrs...	"	Northern Ohio.	8.5	Clear yellow, translucent.	"	"					+					2.3
S. 44.	F. 4 yrs...	"	?	6.0	Clear yellow, translucent.	"	"					+					2.3
S. 67.	? 1 yr.	"	?	7.5	Clear yellow, translucent.	"	"					+					2.6
S. 57.	? 1 yr.	"	?	5.4	Clear yellow, translucent.	"	"					+					3.2
S. 70.	F. 4 yrs...	"	Northern Ohio.	7.0	Clear yellow, translucent.	"	"					+					3.6
S. 69.	F. 3 yrs...	"	Northern Ohio.	8.0	Clear yellow, translucent.	"	"					+					3.6
S. 66.	F. 3 yrs...	"	Northern Ohio.	7.5	Clear yellow, translucent.	"	"					+					3.6
S. 54.	? 1 yr.	Good...	?	6.55	Clear yellow, translucent.	"	"					+					2.8
S. 64	? 1 yr.	"	Northern Ohio.	8.0	Clear yellow, translucent.	"	"					+					3.6
S. 19	M. 2 yrs...	Excellent.	?	52.0	Clear yellow, translucent.	"	"					+					3.6
S. 56	M. 1 yr.	Good...	?	6.4	Clear yellow, translucent.	"	"					+					4.
S. 68.	M. 10 mos.	"	Northern Ohio.	7.5	Clear yellow, translucent.	"	"					+					4.

methods, the colloid series will contain sufficient gradations of the hyperplasias to parallel the normal series throughout and will be discussed with equal emphasis.

These two groups of colloid glands suffice, however, to illustrate, first, the fact that pure colloid glands of the different animals have iodine contents very closely approaching those of normal glands, and, second, that colloid-early glandular hyperplasias have iodine contents similarly close to those with normal-early glandular hyperplasias. We believe that if all the conditions (diet, etc.) could be strictly controlled the iodine content of colloid glands would absolutely parallel those of normal glands and that a like parallelism would be seen throughout the gradations of hyperplasia of both the normal and colloid series.

The probable reasons why we rarely obtain colloid glands in sheep, cattle and hogs are (1) that they are killed at an age when the natural occurrence of colloid glands is rare, and (2) that the conditions of life (as regards habits, food and locality) are more constant than obtain for man or dogs.

So striking a uniformity in the anatomic changes for widely different animals can not be without significance. It suggests that the etiologic factor or factors in the production of thyroid hyperplasia (goiter) are probably the same in all these animals. The constant relation between structure and iodine content suggests that iodine is a common factor in all these animals.

It seems fair to infer from this comparative study of anatomic structure and iodine content that iodine is a very important factor, acting in the same direction and manner in all classes of animals in which hyperplasias (goiterous changes) are observed, and that, therefore, for a general study of goiter, any of the animals mentioned may be used as a basis, and the results be applicable to man.

NOTE.—In conclusion we wish to thank Professors Torald Sollmann and G. N. Stewart for their careful criticisms and suggestions.

Reprinted from The Archives of Internal Medicine
February, 1909

AMERICAN MEDICAL ASSOCIATION, ONE HUNDRED AND THREE DEARBORN AVENUE
CHICAGO

EFFECTS OF THE ADMINISTRATION OR THE WITHHOLD-
ING OF IODIN-CONTAINING COMPOUNDS IN NORMAL,
COLLOID OR ACTIVELY HYPERPLASTIC
(PARENCHYMATOUS) THYROIDS
OF DOGS

SOME EXPERIMENTS ON (CONGENITAL) PRENATAL THYROID HYPERPLASIA
IN DOGS; REMARKS ON THE CLINICAL MANIFESTATIONS
ASSOCIATED WITH MARKED THYROID HYPERPLASIA *

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The observations and experiments here recorded have been made on dogs, and include three with normal, eight with colloid and seventeen with actively hyperplastic glands, as ascertained by the first specimen of thyroid removed. The plan followed has been to remove a control portion of the thyroid from each dog for histologic diagnosis and iodine determination, and at intervals to remove other portions for comparison.

Our experiments may be divided into two groups: (1) those in which iodine was administered and (2) those in which no iodine was administered, except what was contained in a liberal diet of cooked meat, bread, sodium chloride, milk and water. The food being the same in each group, no other remarks are necessary, except that dogs normally store some iodine from such a diet. These two groups have been tabulated, and in presenting Tables 1 and 2 we have arranged the cases according to the anatomic groups represented, as ascertained by the histologic diagnosis of the first specimen of thyroid removed. Thus normal and colloid glands are placed first; then follow in order the several degrees of hyperplasia.

We shall discuss the cases according to the groups represented.

1. *Normal Glands*.—Of the three subjects (A-123, A-26, A-27), only one (A-26) was given iodine directly. In this case the iodine was distinctly but not markedly increased in the remaining lobe. This lobe also increased in size, but remained normal in structure. The other two subjects (A-123 and A-27) showed hyperplasia of the remaining lobes. These three cases show that iodine does have a preventive effect on the

*From the Laboratories of Experimental Medicine and Pharmacology of Western Reserve University.

hyperplasia and also that iodine is increased even in normal glands, though slightly. This is what is expected when one recalls the normally wide variations in the iodine contents of normal glands from all animals.¹ The other point of importance, namely, that glands may grow in size and yet never show any deviation from normal structure, is of considerable interest, in that it furnishes additional proof that hyperplasia, however slight, is no part of the normal growth of normal glands, but must be the evidence of some abnormal factor or stimulus. Further, it shows that the administration of iodine will not prevent the normal growth of a normal gland. Lastly, when the three cases are taken together, it is seen that the amount of thyroid removed is of secondary importance to the iodine content in determining the occurrence of hyperplasia, although iodine does not seem to prevent hyperplasia after a certain maximum of thyroid is removed, just as it does not prevent the normal growth of pups' thyroids. It will be noted that all three dogs were young. This, as Horsley² and all subsequent investigators have shown, is very important, since the needs for the gland's activities are greater in youth. The symptoms following the removal of the thyroid are also greater, and compensatory hyperplasia occurs more constantly and more rapidly the younger the animals are.

Colloid Glands.—There were three cases (A-51, A-120, A-118) in which iodine was given and five cases (A-63, A-95, A-104, A-106, A-122) in which it was not given. In the five cases in which iodine was not given there was a gradual lessening of iodine in the succeeding portions removed, just as in the normal glands. This is in sharp contrast with the hyperplasias, all of which will be seen to have gained slightly in iodine. It suggests that the ability of normal or colloid glands to store iodine from the food is much less than that of actively hyperplastic glands. While in general the iodine contents of colloid glands per gram are less than those of normal glands per gram, this is not necessarily true. The three glands in which iodine was administered show a marked increase in the thyroid iodine, though, as will be seen, it is not as great as that which occurs in the active hyperplasias, thus agreeing with the normal glands in this respect. In two of the cases, A-104 and A-106, secondary (i. e., glands undergoing active hyperplasia for the second time) compensatory hyperplasia occurred, but only after the iodine had been greatly reduced. This also is in harmony with what nor-

1. Marine and Lenhart: Further observations on the relation of iodine to the structure of the thyroid gland in the sheep, dog, hog and ox. *THE ARCHIVES INT. MED.*, 1909, iii, 66.

2. Horsley: *Brit. Med. Jour.*, 1892, i, 215.

mally occurs in the spontaneous secondary hyperplasias. In the case of colloid glands, just as was shown for normal glands, the amount of gland removed does not seem to be so important as is the iodine content in starting the hyperplasia and, also just as in the normal glands, there is a level below which iodine will not protect against secondary hyperplasia. All the evidence taken together indicates that colloid glands behave exactly as normal glands when subjected to the same experiments, or, in other words, that colloid glands parallel normal glands.

Hyperplasias.—Discussing the six cases in which no iodine was directly administered, it will be seen that they represent degrees of hyperplasia from *early* to *moderate*. They all show an increase of iodine in the successive portions removed. This is in sharp contrast with the normal and colloid glands, which under the same conditions of food and experiment did *not* show increases of iodine. Associated with this slight gradual increase in iodine, there is a slow return toward colloid glands. This slow return toward the colloid condition should be contrasted with the rapid return to the colloid condition in those cases given iodine directly.

Taking up the cases of hyperplasia in which iodine was administered, there were eleven, ranging from *normal early* to *marked* glandular hyperplasia. In all these cases very marked and very rapid increases in the iodine contents are shown. Taking the whole series, the general impression is that iodine is stored more rapidly in the cases with marked hyperplasia. This is very evident when colloids or normals are contrasted with the hyperplasias. The form of administration of iodine appears to be of less importance than the degree of hyperplasia in determining the rapidity with which iodine is taken up by the thyroid. The amount of iodine taken up obviously must depend on the quantity administered, the degree of hyperplasia and the extent of the epithelial surface. The rapidity of the involution (reversion) process in subjects given iodine may be judged from A-119 in which noticeable histologic differences were present in five days. This is about the average time required, though we have seen it in three days. The average time required to induce complete involution (reversion) may also be ascertained from this case, in which in 26 days the entire series of changes from marked glandular hyperplasia back to pure colloid gland occurred. How much this may be modified by different methods of administration and different preparations of iodine is yet to be ascertained. Our data indicate that these will be found to be of minor general pharmacologic importance, though probably of great therapeutic importance. Desiccated thyroid preparations appear to have no advantage over the inorganic

TABLE 1.—EXPERIMENTS IN

Case No.	Sex.	Age.	Weight, Kg.	Day, Month, Year of Operation.	Part Removed.	Weight of Thyroid Removed, gm.	Color.	Consistency.	Visible Colloid.	Histologic Diagnosis.
A-26a....	F.	3 mos....	2.4	15, 2, '07..	R. lobe....	0.24	Reddish, transl.	Firm.....	Normal..	Normal.....
A-26b....	F.	4½ mos..	4.0	2, 4, '07...	L. lobe....	0.305	Yellow, transl.	Firm.....	Normal..	Normal.....
A-51a....	M.	Middle...	3.2	29, 3, '07..	L. lobe....	22.1	Reddish, transl.	Moderate..	Reduc'd.	Colloid.....
A-51b....	M.	Middle..	3.0	4, 4, '07...	R. lobe....	23.1	Reddish, transl.	Moderate..	Normal..	Colloid.....
A-120a....	M.	7 mos....	3.6	15, 4, '08..	L. lobe....	1.7	Yellow, transl.	Firm.....	Normal..	Colloid.....
A-120b....	M.	7½ mos..	3.2	2, 5, '08...	R. lobe....	1.1	Yellow, transl.	Firm.....	Normal..	Colloid.....
A-118a....	M.	3 yrs.....	9.0	25, 3, '08..	Part of l. lobe.	2.7	Yellow, transl.	Firm.....	Normal..	Colloid.....
A-118b....	M.	3 yrs.....	9.0	30, 3, '08..	Part of l. lobe.	6.5	Yellow, transl.	Firm.....	Normal..	Colloid.....
A-118c....	M.	3 yrs.....	?	4, 4, '08...	Part of l. lobe.	6.0	Yellow, transl.	Firm.....	Normal..	Colloid.....
A-118d....	M.	3 yrs.....	?	10, 4, '08..	Part of r. lobe.	8.25	Yellow, transl.	Firm.....	Normal..	Colloid.....
A-118e....	M.	3 yrs.....	?	15, 4, '08..	Part of r. lobe.	7.3	Yellow, transl.	Firm.....	Normal..	Colloid.....
A-118f....	M.	3 yrs.....	?	6, 5, '08...	Part of r. lobe.	3.3	Reddish, transl.	Moderate..	Visible..	Colloid.....
A-118g....	M.	3 yrs.....	?	8, 5, '08...	Part of r. lobe.	3.25	Reddish, transl.	Moderate..	Visible..	Colloid early...
A-17a....	F.	Middle...	5.4	22, 1, '07..	R. lobe....	0.7	Gray, transl.	Firm.....	Normal..	Normal early...
A-17b....	F.	Middle...	5.0	15, 3, '07..	L. lobe....	0.65	Clear, transl.	Firm.....	Normal..	Colloid.....
A-18a....	F.	Middle...	5.4	22, 1, '07..	L. lobe....	7.5	Grayish, opaque.	Soft.....	None....	Mod. gland. hyperplasia.
A-18b....	F.	Middle...	3.18	11, 2, '07..	R. lobe....	4.75	Yellow, transl.	Firm.....	Normal..	Colloid.....
A-73a....	M.	Young...	8.6	25, 4, '07..	L. lobe....	2.6	Reddish, opaque.	Moderate..	None....	Moderate gland. hyperplasia.
A-73b....	M.	Young..	7.1	4, 5, '07...	R. lobe....	2.1	Reddish, transl.	Firm.....	Reduc'd.	Colloid, early gland.
A-16a....	M.	Old.....	5.0	22, 1, '07..	L. lobe....	4.15	Grayish, opaque.	Soft.....	None....	Mod. marked gland. hyperp.
A-16b....	M.	Old.....	3.2	20, 2, '07..	R. lobe....	2.7	Yellow, transl.	Firm.....	Normal..	Colloid.....
A-52a....	F.	Pup.	2.7	29, 3, '07..	R. lobe....	3.6	Grayish, opaque.	Soft.....	None....	Mod. marked gland.
A-52b....	F.	Pup.	2.8	22, 4, '07..	L. lobe....	2.0	Clear, transl.	Firm.....	Normal..	Colloid.....
A-55a....	M.	Pup.	7.27	1, 4, '06...	L. lobe....	72.0	Opaque...	Soft.....	None....	Mod. marked gland. hyperp.
A-55b....	M.	Pup.	6.36	8, 4, '09...	R. lobe....	57.2	Gray-red, opaque.	Soft.....	None....	Moderate gland. hyperplasia.
A-125a....	M.	1 yr.....	6.8	9, 5, '08...	Part of l. lobe.	5.8	Grayish, opaque.	Soft.....	None....	Marked gland. hyperplasia.
A-125b....	M.	1 yr.....	6.8	18, 5, '08..	Rem. of l. lobe.	93.0	Grayish, opaque.	Soft.....	None....	Moderate marked gland. hyperplasia.
A-114a....	F.	8 mos....	5.9	19, 2, '09..	R. lobe....	95.0	Grayish-red, opaque.	Soft.....	None....	Marked gland. hyperplasia.
A-114a ² ...	F.	8 mos....	5.9	19, 2, '08..	Accessory thyroid.	5.0	Grayish-red, opaque.	Soft.....	None....	Marked gland. hyperplasia.
A-114b....	F.	8 mos....	5.0	24, 2, '08..	L. lobe....	27.2	Grayish-red, opaque.	Soft.....	None....	Mod. marked gland. hyperplasia.
A-114c....	F.	8 mos....	4.2	26, 2, '08..	R. lobe entire.	23.25	Yellowish, opaque.	Soft.....	Visible..	Colloid, mod. gland. hyperp.

WHICH IODIN WAS GIVEN.

Iodin, per gm., Dried.	Iodin, per gm., Moist.	Amount, Form and Duration of Iodid Administration.	Complicating Factors During Experiment.	Remarks.
2.300	0.380	None.	
3.467	0.705	1 c.c. sat. alc. sol. iodid from 2, 21 to 3, 8, '07.	None.....	Chloroformed to death 4, 2, '07.
0.707	0.188	None.	
0.969	0.245	6 5-gr. tablets desiccated thyroid from 3, 29 to 4, 5, '07.	Pneumonia	Death on 5th day of pneumonia.
2.353	0.400	Distemper and chorea on admission.*	
4.480	1.195	Given 70 gtt. syrup of ferr. iodid from Apr. 16 to May 2.	No apparent improvement in dis- temper and chorea; chloformed to death 5, 2, '08.
0.721	0.186	None.	
1.000	0.237	Given 7.5 gm. of desiccated thyroid containing 1.092 mg. per gm. dried.	None.	
0.477	0.106*	7.5 gm. desiccated thyroid iodid assign'd as above since last opr.	Slight wound in- fection; HgCl ₂ dressing.	Iodin determination uncertain owing to presence of mercury.*
1.815	0.487	120 gtt. syr. ferr. iodid since last operation.	Infection cleared up.	
1.146	0.227	120 gtt. syr. ferr. iodid since last operation.	None.	
0.893	0.171	160 gtt. syr. ferr. iodid from 4, 16, to 5, 1.	None.	
0.126	0.026	No iodid since last operation.	Tetany.	Died 2 days after last operation of tetany.
*	None.....	Iodin not determined — accident — hitch pregnant.*
4.615	1.093	200 mg. iodid given from 1, 26 to 2, 7, '07.	None.....	Killed with chloroform 3, 15, '07.
0.261	0.056	None.	
4.184	1.265	Fed 545 gms. fresh sheep's thyroid from Jan. 25 to Feb. 3.	Emaciation; diar- rhea.	Dog died after great loss of weight, associated with serious diarrhea.
0.420	0.071	Canine chorea; "distemper."	
*	5 gtt. sat. alc. iodin from 4, 26 to 4, 30.	Acute distemper..	No iodin determination; specimen lost.
0.086	0.014	None.	
1.739	0.393	Fed 65 5-gr. tablets in 28 days following 1st operation.	Emaciation.....	Killed with chloroform 2, 20, '07; great loss of weight; slight diar- rhea.
0.413	0.057	None.	
3.196	0.815	15 gtt. sat. alc. sol. iodin from 4, 1 to 4, 11.	None.....	Killed with chloroform.
0.054	0.008	None.	
1.399	0.292	7 gtt. sat. alc. sol. of iodin since April 2.	Pulmonary em- bolism.	Dog died suddenly night of April 8, and autopsy showed the pulmonary artery plugged with an embolus.
0.077	0.016	None.	
2.107	0.453	Wound packed 6 times with iodoform gauze.	Wound infection..	Died suddenly May 18, owing to wound being torn open by another dog in a fight.*
0.000	0.000	None.....	Dog was emaciated, pulse 180, heart action shook entire body, slight diarrhea.
0.000	0.000	None.	
1.123	0.243	120 gtt. syr. ferr. iodid fed from 2, 19 to 2, 24.	Slight wound in- fection.	
1.480	0.352	40 gtt. syr. ferr. iodin in 2 days.	Fatal hemorrhage.	Hemorrhage due to infected silk ligature.

TABLE 1.—EXPERIMENTS IN

Case No.	Sex.	Age.	Weight. Kg.	Day, Month, Year of	Part Removed.	Weight of Thyroid Removed gm.	Color.	Consistency.	Visible Colloid.	Histologic Diagnosis.
A-116a....	F	7 mos....	6.5	13, 3, '08..	R. lobe....	6.5	Grayish, opaque.	Soft.	None....	Marked gland. hyperplasia.
A-116b....	F.	7 mos....	6.0	17, 3, '08..	R. lobe....	11.6	Grayish, opaque.	Soft.	Visible...	Colloid mod. marked gland. hyperplasia.
A-116c....	F.	7 mos....	5.5	21, 3, '08..	R. lobe....	27.6	Yellowish opaque.	Firm.....	Visible...	Colloid mod. marked gland. hyperplasia.
A-116d....	F.	7 mos....	5.5	24, 3, '08..	L. lobe....	43.5	Yellowish, opaque.	Firm.....	Visible...	Colloid early gland. hyperplasia.
A-117a....	M.	2 yrs....	6.9	21, 3, '08..	R. lobe....	4.2	Gray-red, opaque.	Soft.	None. ...	Marked gland. hyperplasia.
A-117b....	M.	2 yrs....	6.6	25, 3, '08..	L. lobe } R. lobe }	67.10	Yellowish, opaque.	Soft.	Just visible.	Colloid mod. marked.
A-119a....	M.	8 mos....	8.4	10, 4, '08..	L. lobe....	9.82	Reddish, opaque.	Soft.	None....	Marked gland. hyperplasia.
A-119b....	M.	8 mos....	8.2	15, 4, '08..	L. lobe....	20.5	Yellowish-red, opaque.	Soft.	Just visible.	Colloid mod. marked gland.
A-119c....	M.	8 mos....	8.0	22, 4, '08..	R. lobe....	1.5	Yellowish, opaque.	Moderate..	Visible...	Colloid mod. gland.
A-119d....	M.	8 mos....	10.0	28, 4, '08..	R. lobe....	7.2	Yellowish, transl.	Firm.....	Normal..	Colloid early gland.
A-119e....	M.	9 mos....	10.5	6, 5, '08..	R. lobe....	6.5	Yellow, transl.	Firm.....	Normal..	Colloid
A-119f....	M.	10 mos....	11.9	15, 6, '08..	Remaind'r of lobes.	1.3	Yellow, transl.	Firm.....	Normal..	Colloid

salts of iodine, or over pure iodine, in inducing these histologic changes. If anything, the pure iodine was taken up more rapidly. Going back to the cases in which iodine was not administered, it will be seen that in sharp contrast with A-119, in which complete involution (reversion) occurred in twenty-six days, A-121 did not reach complete involution (reversion) for sixty-six days.

FORMS, MODE OF ADMINISTRATION AND AMOUNTS OF IODINE ADMINISTERED

We have employed iodoform, fresh sheep's thyroids, desiccated sheep's thyroid, pure iodine, ferrous iodide, all of which forms are followed by the storage of iodine in the glands, whether normals, colloids or hyperplasias. The resulting histologic effect in all is the same, viz.: the return to the colloid or quiescent condition.

As to the mode of administration: It is taken up by the thyroid when "painted" on the skin, given by mouth or injected hypodermically. On this point, however, we do not possess sufficient data to differentiate specifically between the several modes of administration other than that pure iodine apparently is taken up most rapidly.

WHICH IODIN WAS GIVEN—Continued.

Iodid, per gm., Dried.	Iodid, per gm., Moist.	Amount, Form and Duration of Iodid Administration.	Complicating Factors During Experiment.	Remarks.
0.015	0.003	No iodid administered prior to first opera- tion.	None.....	Rhachitic, anemic and somewhat emaciated, with forcible action and pulse 160; eyes weeping and stools soft.
1.000	0.188	120 gtt. syr. ferr. iodid in 4 days since first operation.	Slight wound in- fection.	
2.153	0.477	120 gtt. syr. ferr. iodid in 4 days since 2d operation.	Slight wound in- fection.	
2.691	0.693	80 gtt. syr. ferr. iodid in 3 days.	Fatal hemorrhage.	Hemorrhage due to infected ligature sloughing off a large vein; thymus atrophic; spleen and lymph gland enlarged.
0.065	0.014	No iodid given prior to 1st operation.	None.	
2.384	0.540	120 gtt. syr. ferr. iodid given in 4 days since 1st operation.	Over anesthetized.	Ineffectual efforts at resuscitation.
0.200	0.040	No iodid given prior to 1st operation.	None.....	Anemic, but fat deposits normal.
2.861	0.553	120 gtt. syr. ferr. iodid in 5 days since first operation	None.	
4.078	0.860	300 gtt. syr. ferr. iodid in 7 dys. since 2d ope.	None.	
3.353	0.749	No iodid given since last operation.	None.....	Dog gaining weight rapidly
3.522	0.894	No iodid given.....	None.	
2.770	0.554	No iodid given.....	Killed by negli- gent anesthetist.	An attempt was made June 1, but no thyroid found in a hasty exam. Dog killed June 15 by negligence after operation was completed.

Coming to the amounts of iodin administered, one of the most striking things brought out is that of the minute amounts (minute in contrast with what we had generally seen recommended in the treatment of goiter) necessary to induce thyroid changes. It appears that the more marked the hyperplasia the greater is the amount of iodin taken up, since in normal dogs one can give very large amounts of iodin without inducing any systemic effect or raising the iodin content of the glands any more than much smaller doses do in actively hyperplastic glands. It may be well to refer to the systemic effects produced by iodin as we have seen them.

In the first place, reference to Tables 1 and 2 will show that in normal or colloid glands there is either little change in body weight or there is about the same change whether iodin was administered or not. This is not true of the subjects with hyperplasia. All such subjects when fed iodin lost weight rapidly for a time (one to two weeks), then started to gain, while in those not fed iodin a loss of weight was not observed. We have made some specific experiments regarding the loss of weight. Thus we took three markedly goitrous pups of the same litter, aged six

TABLE 2.—EXPERIMENTS IN WHICH

Case No.	Sex.	Age.	Weight.	Day, Month, Year of Operation.	Part Removed.	Weight of Gland Removed.	Color.	Consistency.	Colloid.
A-27a	F.	3 mos....	1.85	15, 2, '07..	R. lobe	0.15	Reddish, transl.	Firm	Normal....
A-27b....	F.	3 mos....	1.53	2, 4, '07...	L. lobe	0.15	Reddish, transl.	Firm	Reduced ..
A-123a	M.	52 days..	1.4	7, 5, '08...	L. lobe	0.195	Reddish, transl.	Firm	Normal....
A-123b....	M.	3½ mos..	2.5	1, 6, '08...	One-half of r. lobe	0.100	Reddish, transl.	Firm	Normal....
A-123c....	M.	8½ mos..	8.1	7, 12, '08..	All of r. lobe..	0.600	Gray, red.	Moderate..	None
A-63a	F.	Middle.*	12.7	17, 4, '07..	L. lobe	14.25	Yellowish, transl.	Firm	Normal....
A-63b....	F.	Middle..	12.7	22, 5, '07..	R. lobe	14.00	Yellowish, transl.	Firm	Normal....
A-95a	F.	Middle..	5.9	11, 5, '07..	L. lobe	5.1	Yellowish, transl.	Firm	Normal. ..
A-95b....	F.	Middle..	5.7	6, 6, '07...	R. lobe	3.4	Yellowish, transl.	Firm	Normal....
A-104a	F.	Middle..	7.71	10, 9, '07..	R. lobe	1.7	Yellowish, transl.	Firm	Normal....
A-104b....	F.	Middle..	7.7	4, 1, '08...	Part of l lobe.	1.45 2.25	Reddish, transl.	Firm	Visible....
A-104c....	F.	Middle..	7.7	7, 1, '08...	Remains of l. lobe.	0.230	Reddish, transl.	Firm	Visible....
A-106a	F.	Middle..	11.8	5, 6, '07...	R. lobe	29.5	Clear, brownish-yellow.	Firm	Normal....
A-106b....	F.	Middle..	9.52	15, 7, '07..	½ l. lobe.....	15.0	Clear, brownish-yellow.	Firm	Normal....
A-106c....	F.	Middle..	9.50	10, 9, '07..	½ of remaining part of l. lobe.	3.0	Reddish, yellow.	Moderate..	Reduced...
A-106d....	F.	Middle..	7, 12, '07..	Remains of l. lobe.	4.5	Reddish, opaque.	Soft	Just visible.
A-122a	F.	2 mos....	1.8	7, 5, '08...	Part of l. lobe.	2.2	Yellow, transl.	Firm	Normal....
A-122b....	F.	21, 5, '08..	Part of l. lobe.	2.5	Yellow transl.	Firm	Normal....
A-122c....	F.	2.3	1, 6, '08...	Part of l. lobe.	1.0	Yellow, transl.	Firm	Normal....
A-122d....	F.	12, 6, '08..	Part of l. lobe.	1.8	Yellow, transl.	Firm	Normal....
A-122e....	F.	3 mos....	2.9	17, 6, '08..	Entire r. lobe.	10.5	Yellow, transl.	Firm	Normal....
A-64a	M.	Pup.	2.9	17, 4, '07..	L. lobe.....	2.25	Reddish, opaque.	Moderate..	Reduced ..
A-64b....	M.	4.1	5, 6, '07...	R. lobe.....	2.3	Reddish, transl.	Firm	Normal....
A-94a	F.	Middle..	2.15	11, 5, '07..	L. lobe.....	1.5	Reddish, transl.	Firm	Normal....
A-94b....	F.	Middle..	1.95	25, 5, '07..	R. lobe.....	1.0	Reddish, transl.	Firm	Normal....
A-112a	F.	Young adult.	5.4	15, 1, '08..	L. lobe and ⅔ of r. lobe.	4.15	Reddish, transl.	Moderate..	Reduced ..
A-112b....	F.	Young adult.	5.4	25, 3, '08..	Part of r. lobe.	?	Reddish, transl.	Firm	Normal....
A-112c....	F.	Young adult.	5.9	7, 12, '08..	All of r. lobe..	0.250	Reddish, opaque.	Moderate..	Visible....
A-74a	F.	Young...	5.44	25, 4, '07..	L. lobe.....	3.6	Reddish, opaque.	Moderate..	Reduced ..
A-74b....	F.	Young...	6.35	1, 6, '07...	R. lobe.....	2.8	Reddish, opaque.	Moderate..	Reduced ..
A-126a	M.	?	2, 6, '08...	L. lobe.....	13.0	Reddish, transl.	Moderate..	Visible....
A-126b....	M.	2 years..	?	29, 6, '08..	Remains of r. lobe.	3.3	Reddish brown.	Moderate..	Visible....

IODIN WAS NOT GIVEN.

Histologic Diagnosis.	Iodin per gm., dried.	Iodin per gm., Moist	Complicating Factors in Experiment.	Remarks.
Normal.....	0.886	0.248	None.	
Early gland. hyper- plasia.	1.520	0.253	Pneumonia.	
Normal.....	6.921	1.384	None.	
Normal.....			None.	
Marked gland. hy- perplasia.	0.115	0.025	None.	
Colloid.....	1.246	0.298	None.....	*
Colloid.....	0.323	0.092	None.....	Killed 5, 22, '07.
Colloid.....	1.076	0.251	None.	
Colloid.....	0.719	0.163	None.....	Killed with chloroform 6, 6, '07.
Colloid.....	2.738	0.510	None.....	Bitch gave birth to 5 pups 5, 17, '07. Im- pregnated again 9, 7, '07.
Colloid, early gland.			Tetany.....	Died 1, 7, '07 of tetany.
Colloid.....	0.308	0.033	None.	
Colloid.....	0.554	0.066	None.	
Colloid, mod. gland. hyperplasia	0.554	0.099	None.	
Colloid, mod. gland. hyperplasia.	0.115	0.022	Probably myx- edema.	Bitch died 1, 21, '08—1½ months after last operation. Accessory thyroids present.
Colloid.....	1.520	0.370	None.....	On admission neck brown from iodine.
Colloid.....	1.350	0.384	None.	
Colloid.....	1.621	0.437	None.	
Colloid.....	1.262	0.350	None.	
Colloid, gland.....	1.615	0.361	None.....	Killed June 17 by another dog; neck ter- ribly torn and r. thyroid lobe hanging from wound.*
Early gland. hy- perplasia.	0.300	0.051	None.	
Colloid.....	2.326	0.451	None.....	Killed with chloroform 6, 6, '07.
Early gland. hyper- plasia.	0.657	0.122	None.	
Early gland. hyper- plasia	1.024	0.215	HgCl ₂ poisoning.	Died May 25 of acute HgCl ₂ poisoning.
Early mod. gland. hyperplasia.	0.332	0.078	Pregnant.	
Colloid.....			Pregnant.....	Gave birth to 2 pups 3, 15, '08. Gave birth to 5 pups 10, 29, '08.
Colloid, mod. mark- ed gland. hyper- plasia.	0.128	0.030	None.....	Tetany developed during second pre- gnancy; controlled by CaCl ₂ ; developed myxedema after last operation
Mod. gland. hyper- plasia.	0.521	0.072	None.	
Colloid, early gland. hyperplasia	1.452	0.275	None.....	Killed with chloroform 6, 1, '07.
Colloid, mod. gland. hyperplasia.	0.448	0.098	None.	
Colloid, early mod gland. h'perplasia.	0.560	0.114	Slight wound in- fection; cleared up quickly.*	Died while taking ether at 2d operation

TABLE 2.—EXPERIMENTS IN WHICH

Case No.	Sex.	Age.	Weight	Day, Month, Year of Operation.	Part Removed.	Weight of Gland Removed.	Color.	Consistency.	Colloid.
A-121a ...	M.	Middle.	7 3	22, 4, '08..	Part of r. lobe	4.6	Reddish Yellow.	Moderate..	Visible...
A-121b....	M.	Middle.	28, 4, '08..	Part of r. lobe.	7.6	Reddish yellow.	Moderate..	Visible....
A-121c ...	M.	Middle.	9, 5, '06...	Part of r. lobe.	6.4	Reddish, transl.	Moderate..	Visible....
A-121d....	M.	Middle.	21, 5, '08..	Part of l. lobe.	3.6	Reddish, transl.	Moderate..	Normal....
A-121e ...	M.	Middle.	8 7	2, 6, '08...	Part of l. lobe.	1.2	Reddish, transl.	Moderate..	Normal....
A-121f ...	M.	Middle.	12, 6, '08..	Part of l. lobe.	4.85	Reddish, transl.	Moderate..	Normal....
A-121g ...	M.	Middle.	27, 6, '08..	Part of l. lobe.	4.2	Reddish, transl.	Moderate..	Normal....
A-121h....	M.	Middle.	10, 7, '08..	Part of l. lobe.	2.0	Reddish, transl.	Moderate..	Normal....
A-121i ...	M.	Middle.	10.9	13, 9, '08..	Part of l. lobe.	0.5	Reddish, transl.	Moderate..	Reduced ..
A-121j ...	M.	Middle.	12.1	1, 1, '08...	Part of l. lobe.	0.8	Reddish, transl.	Moderate..	Normal....
A-121k....	M.	Middle.	12.0	22, 12, '08.	Part of l. lobe.	0.855	Gray, red, transl.	Moderate..	Reduced ..

weeks; one was fed pure iodine by mouth, one ferrous iodide by mouth, and the other was kept as a control. We also took three pups raised in the laboratory with histologically normal glands and fed the same amount and kinds of iodine to them. In the goitrous pups the loss of weight was very rapid (one-twelfth of body weight in five days) in those fed iodine, and one-fortieth in the pup used as a control. On the other hand, the normal pups continued to gain in weight, whether fed iodine or not.

This brings up a very important, though well-known, observation, namely, that iodine administered to dogs with hyperplastic thyroids has a physiological action like the desiccated thyroid; i. e., it rapidly reduces the body weight, while iodine administered to normal dogs does not. Without further data than our anatomic observations we advance the following possible explanation for this phenomenon, which has long been known to students of human goiter: In the hyperplastic glands their ability to take up iodine is greatly increased, owing to the greatly increased blood supply and the increased epithelial surfaces of the gland, and the excretory apparatus (whether through the venous or lymph channels) is also greatly increased so that the ability of the gland to give off the iodized protein substance is increased to practically the same extent as is the ability to take iodine from the blood, and until this excretion can be lessened the organism is receiving, in effect, excessive doses of the physiologically active substance. As will be recalled from the anatomic

IODIN WAS NOT GIVEN—Continued.

Histologic Diagnosis.	Iodin per gm., Dried.	Iodin per gm., Moist.	Complicating Factors in Experiment.	Remarks.
Colloid, mod. gland. hyperplasia.	0.269	0.059	None.	
Colloid, mod. gland. hyperplasia.	0.455	0.099	None.	
Colloid, early mod. gland. hyperplasia.	0.692	0.167	None.	
Colloid, early gland. hyperplasia.	1.838	0.520	None.	
Colloid, early gland. hyperplasia.	1.774	0.446	None.	
Colloid, early gland. hyperplasia.	1.427	0.369	None.	
Colloid.....	2.170	0.550	None.	
Colloid, early gland. hyperplasia.	1.091	0.188	None.	
Colloid, early gland. hyperplasia.	1.082	0.196	None.	
Colloid.....	1.925	0.513	None.....	From 10, 3, '00, to 10, 25, '08, dog was given 15 c.c. syr. ferr. iodid by mouth. Histology: Colloid gland.
Colloid, early gland. hyperplasia.	1.540	0.305	None.....	Developed tetany 12, 27, '08; controlled by CaCl_2 and, save for tetany, in excellent condition 1, 26, '09.

studies, the body proceeds to accomplish this end by gradually inducing obliterating endarteritis accompanied by a lessening of the size of the veins and lymphatic channels from the gland so that these changes are quite evident when the gland has reached the colloid state. (This process has also been recognized and described by v. Bruns,³ by Oelsner⁴ and De Ligneris.⁵) And, as is well known, the administration of small doses of iodine (not in the form of desiccated thyroid) to normal or colloid glands does not occasion a noteworthy loss of weight. Indeed, clinically, in dogs it induces an increase in weight. Whether these anatomic changes in the vessels accompanying the process of involution (reversion) may be interpreted truthfully as we have here hypothesized is for future experiment and observation to decide. It is, indeed, very suggestive of such a physiologic rôle and may be made use of in clinical experiments with advantage, as we have already done, namely, that of beginning with very small doses of iodine in the hyperplasias and gradually increasing the dosage as the glands approach the quiescent or colloid state. We may add also that in exophthalmic goiter we have used the same method and with it have not seen the well-known untoward effect of

3. Bruns: Beitr. z. klin. Chir., 1896, xvi, 521.

4. Work done under T. Kocher and referred to by him in Arch. f. klin. Chirurg., 1908, lxxxvii, 131.

5. De Ligneris: Dissertation, Berne, 1907.

either desiccated thyroid or of iodine, as these substances usually have been administered in such cases. Thus iodine has a powerful drug action, this action varying with the dosage and with the degree of active hyperplasia of the thyroid and in its administration in all cases of goiter, whether in man or animals, two points should always be borne in the mind, viz.: (1) Small doses of iodine accomplish better thyroid effects than larger doses, whether the gland is normal, colloid or hyperplastic; (2) and, while in normal or colloid glands large doses of iodine (not in the form of desiccated thyroid) usually have no untoward thyroid effects, in the case of actively hyperplastic glands the dose must always be inverse to the degree of thyroid hyperplasia.

To sum up, then, we have observed:

1. The tendency of all active hyperplasias is to revert spontaneously to colloid glands, and this change is hastened or delayed by the presence or absence of iodine. The amount of iodine given is of little consequence in normal and colloid glands, but of the greatest significance in the active hyperplasias.

2. The ability of the glands to take up iodine does not depend so much on the form, mode or amount of its administration as it does on the degree of active thyroid hyperplasia.

3. There is a minimum amount of thyroid tissue below which iodine does not protect against compensatory hyperplasia. This limit is roughly the same whether colloid or normal gland.

It is probable that desiccated thyroid would further inhibit the hyperplasia, though we have no experiments on this point. Such a finding would add to the general belief that there are other activities of the thyroid than that associated with the elaboration of the iodized protein.

EXPERIMENTAL CONGENITAL HYPERPLASIA OF THE THYROID IN DOGS

So far as is known to us, Halsted⁶ was the first to produce and to recognize the experimental production of congenital thyroid hyperplasia in dogs. His observations were made in 1888-9 and included three litters of goitrous pups from three different bitches. All these bitches had had part of their thyroids removed (from one to one and a third lobes) prior to impregnation. The thyroids were, in two litters, twenty times and, in the other, about twelve times larger than normal pups' thyroids. These pups' thyroids showed no differentiation into colloid containing alveoli, as is the case in normal glands, but in general the alveoli were small, undistended tubular structures, lined with cubical

6. Johns Hopkins Hosp. Rep., 1896, i, 399.

epithelium. The whole structure much resembled that of the parathyroid gland.

Following this, Edmunds⁷ was able to get a similar result in one experiment. Thus far we have seen no records of attempts to produce litters of normal pups from bitches which have previously given birth to goitrous ones, or *vice versa*. It is on this phase of the subject that we wish to record our observations.

Dog A-17.—A female dachshund admitted Jan. 20, 1907, weight 5.4 kg. Excellent condition. Thyroid lobes not palpable.

Jan. 22, 1907: Under ether anesthesia the right lobe was removed, weighing 0.7 gm. Excellent recovery. Gross description of the gland removed: Firm, yellowish translucent, colloid visible. Normal vascularity.

Histologic Diagnosis.—Normal-early glandular hyperplasia. Iodin determination not made. (Specimen lost by accident).

Jan. 26, 1907: Wound healed.

January 26 to February 7 inclusive: 200 mg. of iodine were given in the food.

February 22, five pups were born, one still-born. The subsequent histories of these five pups are tabulated in Table 3.

TABLE 3.—PUPS OF DOG A-17.

No. of Puppy.	Weight. Gm.	Sex.	Age.	Day, Month, Year of Operation.	Portion of Thyroid Removed.	Histologic Diagnosis.	Iodin Content.	Remarks.
A-17a...	212	?	0	Normal fetal thyroid.	?	Still-born.
A-17β.	210	F.	3 days.	25, 2, '07.	Both lobes.	Normal fetal thyroid.	Trace.....	Died 18, 2, '07; unable to nurse.
A-17γ.	290	?	9 days.	3, 3, '07...	Left lobe.	Normal fetal thyroid.	Trace.....	Died 4, 3, '07.
A-17δ.	290	F.	9 days.	3, 3, '07...	Right lobe.	Normal fetal thyroid.	?	Died 9, 3, '07; wound infection.
A-17ε...	?	M.	26 days.	Autopsy.	Both lobes.	Normal.	?	Died 20, 3, '07; ker- osene poisoning.

March 15: The mother had scabies; had lost some weight. Dog was chloroformed to death. Weight at death 5 kg. Left lobe of thyroid was removed at autopsy; weight, 0.65 gm.

Gross Description of Left Lobe.—Yellowish, translucent. Abundant colloid. Capsule and vessels normal.

Histologic Diagnosis.—Pure colloid gland (goiter).

Iodin per gm., dry = 4.615 mg. Iodin per gm., fresh = 1.093 mg.

Dog A-104.—Mongrel fox terrier admitted May 16, 1907. Pregnant. Weight, 7.71 kg. Good condition. The thyroid lobes were not palpable.

May 17: Five pups born.

May 21: Four pups alive and in good condition.

August 27: All pups in good condition.

The subsequent histories of these pups are tabulated below.

September 7: Bitch impregnated by non-goiterous fox terrier.

September 10: Under ether anesthesia the entire right lobe, weighing 1.7 gm., and approximately two-thirds of left lobe, weighing 1.45 gm., were removed.

7. Lancet, London, 1901, i, 1451.

Gross Description of Gland Removed.—Yellow, translucent. Consistency firm. Vascularity normal. Capsule thin and delicate. Colloid abundant.

Histologic Diagnosis.—Pure colloid gland (goiter).

Iodin per gm., dry = 2.739 mg. Iodin per gm., fresh = 0.510 mg.

September 16: Dressings removed. Wound healed; had had no evidence of tetany.

October 21: Bitch pregnant.

TABLE 4.—PUPS OF DOG A-104, FIRST LITTER.

No. of Puppy.	Day, Month, Year of Operation.	Age.	Sex.	Weight, Kg.	Portion and Weight of Thyroid Removed.	Histologic Diagnosis.	Remarks.
Pup 1 (T-15).	27, 8, '07.....	102 days.	F.	1.6	Left and $\frac{1}{2}$ of right lobe.	Normal.....	Ether anesthesia.
Pup 1 (T-15).	4, 1, '08.....	232 days.	F.	3.2	Remainder of rt. lobe, 0.150 gm.	Early gland. hyperplasia.	Ether anes.; died 7, 1, '08; tetany.
Pup 2 (T-24).	6, 9, '07.....	112 days.	M.	2.8	Lt. lobe, 0.350 gm. $\frac{1}{4}$ rt. lobe, 0.050	Normal.....	Ether anesthesia.
Pup 2 (T-24).	4, 1, '08.....	232 days.	M.	6.4	Part of rt. lobe, 0.275 gm.	Early gland. hyperplasia.	Ether anesthesia.
Pup 2 (T-24).	20, 12, '08.....	279 days.	M.	7.0	Remainder of rt. lobe, 0.150.	Mod. gland. hyperplasia.	Distemper — chloroformed
Pup 3 (T-25).	6, 9, '07.....	112 days.	F.	1.8	Left lobe, 0.350.	Normal.....	Ether anesthesia.
Pup 3 (T-25).	30, 10, '07..... (Autopsy.)	139 days.	F.	2.6	Right lobe, 0.375.	Mod. gland. hyperplasia.	Killed by another dog.
Pup 4 (T-51).	17, 10, '07..... (Autopsy.)	153 days.	M.	2.3	Left lobe, 0.700..	Normal.....	Killed by another dog. (Kept as control.)

November 9: Whelped four pups, the subsequent histories of which are tabulated in Table 5.

December 22: Bitch in excellent condition.

January 4, 1908: Under ether anesthesia a part of the remaining portion of the left lobe, weighing 2.25 gm., was removed, leaving a piece of thyroid tissue about the size of a small pea. The parathyroid was not seen.

TABLE 5.—PUPS OF DOG A-104, SECOND LITTER.

No. of Puppy.	Day, Month, Year of Operation.	Age.	Sex.	Weight, Gm.	Portion and Weight of Thyroid Removed.	Histologic Diagnosis.	Remarks.
Pup 1 (T-73).	14, 11, '07. (Autopsy.)	5 days..	F.	320.0	Both lobes, 0.105 gm.	Early gland. hyperplasia.	Chloroformed. (Control.)
Pup 2 (T-96).	7, 12, '07 (Autopsy.)	28 days..	F.	960.0	Both lobes, 0.400.	Early gland. hyperplasia.	Killed by another dog.
Pup 3 (T-97).	7, 12, '07. (Autop-y.)	28 days..	F.	910.0	Both lobes, 0.305.	Early gland. hyperplasia.	Killed by another dog.
Pup 4 (T-2).	24, 12, '07. (Autopsy.)	45 days..	F.	1,110	Both lobes, 0.450.	Mod. gland. hyperplasia.	Killed by another dog.

Gross Description of Gland Removed.—Quite firm and vascular and showed considerable regeneration of the thyroid beyond the old suture line. Color red-translucent. Colloid visible.

Histologic Diagnosis.—Colloid-early glandular hyperplasia. No iodine determination.

Jan. 7, 1908: Dog died during the night of tetany. Autopsy showed evidence of salivation. Gastric dilatation. Other tissues normal. Remaining piece of thyroid weighed 0.230 gm. and on histologic examination the ligature was found to have included and caused necrosis of what was probably the only remaining parathyroid.

Dog A-112.—Female mongrel, admitted Jan. 11, 1908. Weight, 5.3 kg. Nutrition good. Thyroid lobes not enlarged.

January 12: Impregnated by a healthy fox terrier.

January 15: Under ether anesthesia the whole left and approximately two-thirds of the right lobe were removed. The total gland removed weighed 4.15 gms. Good recovery.

Gross Description of Gland Removed.—Dark red in color. Moderate consistency. Colloid barely visible. Lobes appear somewhat enlarged. Moderately vascular.

Histologic Diagnosis.—Moderate glandular hyperplasia.

Iodin per gm., dried = 0.332. Iodin per gm., fresh = 0.078.

January 18: Jaws slightly swollen; otherwise condition good.

January 20: Swelling of jaws had disappeared. Appetite good.

January 22: Bandage and stitches removed. Wound healed. The dog received no iodine except what might have been obtained from the food.

March 15: Two pups were born, one still-born; mother in good condition. The histories of these pups are tabulated in Table 6.

TABLE 6.—PUPS OF DOG A-112, FIRST LITTER.

No. of Puppy.	Day, Month, Year of Operation.	Age.	Sex.	Weight, Gm.	Portion and Weight of Thyroid Removed.	Histologic Diagnosis.	Remarks.
Pup 1.....	15, 3, '08 (Autopsy.)	0	?	280.0	Fetal type of hyperplasia.	Still-born.
Pup 2.....	7, 5, '08	52 days..	M.	1.35	Left lobe, 0.195.	Colloid.....	Fed iodine; ether anesthesia.
Pup 2.....	1, 6, '08	77 days..	M.	?	½ of right lobe, 0.100.	Colloid.....	Fed iodine; ether anesthesia.
Pup 2.....	7, 12, '08	267 days.	M.	8.1	Remainder of rt. lobe, 0.600.	Colloid—marked gland. hyperplasia.	11, 3, '09, no tetany, no myxedema, normal.

March 25: Under ether anesthesia approximately one-half of the remaining portion of the right lobe was removed. Recovery from operation good. Piece removed had a normal gross appearance.

Histologic Diagnosis.—Pure colloid gland (goiter). No iodine determination.

March 26, 9 a. m.: Dog in violent tetany. Respiration 180-200 per minute. Mouth gaping. Pulse could not be counted. Tongue protruding and of a very bright red color. Profuse salivation. Dog lay on its side. All muscles tense with intermittent general tetanic seizures. Was given 5 c.c. of a 5 per cent. calcium chlorid solution in one-half pint of milk by a stomach-tube. At 4 p. m. dog was able to walk, though very weak.

March 27: Repeated the dose of calcium chlorid with milk. Dog still had slight muscular twitchings. Respiration 32. Pulse 130.

April 1: Calcium chlorid stopped. Apparent recovery from tetany. Bandage removed, together with stitches. Wound healed.

April 6: No evidence of tetany, though five days have elapsed since calcium chlorid was stopped.

July 3: Dog and pup in good condition. No evidence of scabies, but a prophylactic application of sulphur ointment was given.

September 1: Dog in excellent condition.

October 1: Sulphur ointment again applied.

October 15: Dog pregnant.

October 29: Gave birth to five pups.

October 30: One pup, weight 115 gm., chloroformed to death. Thyroid lobes histologically normal.

November 2: One pup, weight 260 gm., chloroformed to death. Thyroid lobes histologically normal.

November 3: Mother in violent tetany, given 50 c.c. of a 5 per cent. solution of calcium chlorid with relief in two hours.

November 19: No tetanic symptoms since November 3. 5 c.c. of calcium chlorid solution had been given daily.

December 3: Mother and three pups normal. Had weaned the pups.

Summarizing these cases, we find that A-17 gave birth to normal pups after one lobe had been removed and iodine administered. The remaining lobe returned to the colloid state, while the first lobe removed was histologically a *normal-early* glandular hyperplasia.

In A-104 a litter of normal pups was born shortly after admission; then after nearly four months the dog was again impregnated and one and two-thirds thyroid lobes removed, which histologically were pure colloid glands. In the second litter, the pups' thyroids were slightly enlarged and histologically were in a state of early glandular hyperplasia. The remaining portion of the mother's thyroid had also undergone hyperplasia.

In A-112, immediately after impregnation, one and two-thirds lobes were removed, which histologically were in the state of moderate glandular hyperplasia. Of the two pups born, one died at birth and its thyroid was slightly enlarged and histologically showed only cylinders of columnar cells, with no evidence of colloid (fetal type of hyperplasia likened by Halsted to parathyroid tissue). The mother and pup were given iodine. The pup was reared. The second litter of pups from this bitch (A-112) was normal.

These cases, in so far as they show a repetition of Halsted's results, are positive, but they are only suggestive of the inhibiting effect of iodine. They do not eliminate the possibility and, indeed, the probability of other factors than iodine as determining the fetal thyroid reaction. We believe that iodine is the greatest single factor, but that the general food and the general hygienic surroundings are also of great importance, since all the cases of congenital goiter examined show general nutritional disturbances, as anemia, bone changes, etc. Such cases in human pathology have usually been included under "fetal rickets." This fetal thyroid hyperplasia, so far as our observations have extended, seems to

be identical in its anatomic and physiologic characteristics with compensatory hyperplasia following partial removal, and it is likewise identical histologically with the naturally occurring hyperplasias, whether of prenatal or postnatal origin. Iodin has similar inhibiting and involuting (reverting) effects in all these forms of hyperplasia.

Finally, it seems advisable to add some account of the clinical phenomena accompanying these various anatomic conditions of the thyroid, in order that the rather disconnected anatomic, chemical and general biologic data discussed on the preceding pages may be utilized for clinical inference. Again the anatomic grouping must be followed.

1. *Normal Glands*.—Animals with normal thyroids obviously do not concern us.

2. *Colloid Glands*.—Animals with colloid glands are, as a rule, adults (unless treated) and present no symptoms referable to the thyroid, save that the glands are usually enlarged, and, for this reason, one may observe mechanical (pressure) effects, although in quadrupeds this is extremely rare. All animals (sheep and dogs) whose glands were pure colloid were clinically in excellent health. This applies to the colloid glands experimentally produced (by the direct administration of iodine, by food or otherwise), as well as the natural occurring ones.

3. *Hyperplasias*.—The great majority of all animals (sheep, dogs, cats, horses, hogs and cattle) whose glands were histologically in the state of active hyperplasia showed no symptoms which would distinguish them from normal animals by the ordinary methods of examination. This statement is of importance when one recalls that 90 per cent. of the dogs and 50 per cent. of the sheep and cattle of this locality show hyperplastic changes of a greater or lesser degree. On the other hand, there is a degree of hyperplasia which, when present, is always accompanied by clinical manifestations. These clinical manifestations are of different degrees, reaching their highest in the true cretins which die shortly after birth, thence shading off gradually to the limit of detectability. We have used the term "cretinoid" in order to include the several degrees of severity of the symptoms.

All these animals are young (calves, lambs or puppies). In the worst forms the animals die immediately after birth. Such subjects show poorly developed, hairy coats (thin, coarse), a high degree of anemia and deficient calcification of the bones, but with no reduction in the subcutaneous fatty tissue. These animals, as a rule, have much-enlarged thyroids of the glandular-vascular type with prominent lymph glands, thymus and spleen. In dogs, the most common types at the laboratory have been the less severely affected subjects—those which

would eventually recover spontaneously. Farmers in Michigan have told us that lambs usually recover if able to suckle. We have found the same to be true of dogs. In these milder cases one notes the following characteristics: The hair is dry, coarse and partially furred. The palpebral fissure is narrow. The eyes are weeping and dull. The heart is hypertrophied. The rate is rapid and the beat forcible. On slight exertion, back pulsation in the neck veins occurs and the thyroid lobes become acutely swollen with blood. This may produce syncopal attacks in which the animal may die. The epiphyses of the bones are enlarged. The mucous membranes are very pale, almost blanched. So far as we have observed, the appetite is good and the general body bulk is quite or above the average weight. The gait is slow, unsteady, awkward, and mentally they are extremely dull. We have never observed true exophthalmos, although we have imagined in some cases that the eyes were slightly more prominent than in normal pups. These two types illustrate the severest and the moderate degrees. The milder forms down to clinically normal dogs show the same kind of manifestations, the difference being of degree. Excellent and much fuller descriptions of the phenomena in lambs and calves may be obtained from reports by Davis,⁸ Seligmann⁹ and Campbell.¹⁰

8. Davis: Vet. Jour. and Ann. Comp. Path., 1898, xlvii, 25.

9. Seligmann: Tr. Path. Soc. Lond., 1903-4, iv, 1.

10. Campbell: Tr. Med. and Phys. Soc., Calcutta, 1833-4, vii, 1.

Reprinted from The Archives of Internal Medicine
September, 1909, Vol. 4, pp. 253-270

AMERICAN MEDICAL ASSOCIATION
 FIVE HUNDRED AND THIRTY-FIVE DEARBORN AVENUE
 CHICAGO

RELATION OF IODIN TO THE STRUCTURE OF HUMAN THYROIDS

RELATION OF IODIN AND HISTOLOGIC STRUCTURE TO DISEASES IN GENERAL;
TO EXOPHTHALMIC GOITER; TO CRETINISM AND MYXEDEMA*

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INTRODUCTION

Throughout the course of our studies on the formation of goiter it has been our aim to collect all the data possible as to the incidence, kinds and nature of the thyroid changes in animals so that when human thyroid changes were taken up at least some fundamental conclusions could be available as a point of departure. Nevertheless, while the supplanting of indirect and accidental observations on man by the direct observations on animals is the modern and logical way of approaching a medical problem, proper regard must always be had for the difference arising out of the different positions of the different animals in the biological scale of animal life, even though evidence is fast accumulating that their pathology is quite as applicable to man as their physiology, considering their position in the biological scale. This method of approach is particularly desirable in the case of the thyroid, since the advance of our knowledge of thyroid diseases has been restricted by attempting to use human material as a basis of study. This is due (apart from the indirect and accidental nature of such observations) to the fact that complicating factors are so common and modifying conditions so frequent that pure types are not encountered with sufficient frequency in the experience of any one observer to enable him to emphasize their importance.

In the present work we first attempted to use human material, but were forced to turn back and study series of dog, sheep, pig and ox thyroids in order to find basic types of anatomical changes. Therefore, the observations on human thyroid changes are compared with similar changes occurring in the above-mentioned animals. The results of these comparisons have shown a surprising uniformity both in the iodine content and in the histological structure for all these animals—man, dog, sheep, ox and pig.

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ANATOMICAL CLASSIFICATION

The confusion that at present exists throughout all phases of thyroid changes can be inferred from the vast literature that has arisen around one phase—namely, exophthalmic goiter—in the endeavor to establish the fact that in every true case of this disease there occurs active hyperplasia of the thyroid. And, even in this single phase, there are still widely different opinions. All the other phases of thyroid changes are more or less indefinite.

Virchow¹ fully recognized the confusion existing at that time and the errors to which it was leading when he wrote: "With reference to true goiter the opinion has long been held that it comprises a series of definite species (*struma lymphatica*, *cystica*, *ossea*, *vasculosa*, etc.) which develop independently of each other. This is wrong. All these so-called varieties are none other than different modes of development of essentially the same form of goiter. They mean only different forms of terminal conditions or metamorphoses which can be combined with one another in the same tumor, and a very large and striking variety of these metamorphoses may exist in the same tumor."

Since Virchow wrote these words the advent of operative removal of goiters and the extensive reports based on this highly complicated material have in general tended to complicate the classification further. Two major causes have assisted in this confusion. First, as Virchow pointed out, the secondary or complicating changes have been raised to the importance of the primary changes—for example, such terms as "fibrous," "cystic" or "hemorrhagic" goiter have been placed on the same plane with parenchymatous (actively hyperplastic) goiter. Second, in the correlation of the clinical phenomena with the anatomical changes and the development of the clinical-pathological classification the fact has not always been borne in mind that very great anatomical changes may occur in a short space of time and that the clinical phenomena do not necessarily change to the same extent; as, for example, the typical active thyroid hyperplasia of exophthalmic goiter may revert to a pure colloid condition within a month and the clinical picture remain that of a well-defined case of exophthalmic goiter. We have repeatedly observed this change.

In the lower animals where these various secondary or complicating factors are reduced to a minimum it is quite easy to convince oneself by examining any large series of glands that there are fundamental types of thyroid changes concerned in the production of true goiter.

1. Virchow. *Die krankhaften Geschwülste*, 1863, iii, 4.

These fundamental types are (1) the normal thyroid, (2) the actively hyperplastic thyroid (all degrees) and (3) the colloid thyroid.

With these fundamental types established, the problem of bringing the human thyroid changes into relationship with them is not difficult, although there remains in any large series of human thyroids and, to a lesser extent, of dogs' thyroids, a considerable group of glands in which the anatomical changes are so extensive and complicated as to bear little resemblance to the primary types. This is especially true of the human operative material, in which uncomplicated forms are seen only in the active hyperplasias of childhood, puberty, pregnancy and exophthalmic goiter or in the colloid glands resulting immediately therefrom.

From an anatomical material consisting of 370 human, 850 dog, 70 sheep, 67 ox and 26 pig thyroids which we have personally collected and examined, together with a fair review of the literature, the following general schema of anatomical changes has been deduced:

- I. Normal Thyroid.
- II. Active Hyperplasias.
 1. Prenatal—may terminate in:
 - (a) Fibrosis-atrophy.
 - (b) Colloid.
 2. Childhood—may terminate in:
 - (a) Fibrosis-atrophy.
 - (b) Colloid.
 3. Puberty—may terminate in:
 - (a) Exophthalmic goiter, fibrosis-atrophy.
 - (b) Colloid.
 4. Pregnancy—may terminate in:
 - (a) Exophthalmic goiter, fibrosis-atrophy.
 - (b) Colloid.
 5. Exophthalmic goiter—may terminate in:
 - (a) Fibrosis-atrophy.
 - (b) Colloid.
- III. Colloid glands.
 1. Active hyperplasia.
 - (a) Simple hyperplasia—may terminate in:
 - (i) Exophthalmic goiter.
 - (ii) Colloid.
 - (b) Exophthalmic goiter—may terminate in:
 - (i) Fibrosis-atrophy.
 - (ii) Colloid.
 - (c) Colloid.
- IV. Atrophies.
 1. Infantile.
 2. Supervening in exophthalmic goiter, tuberculosis, obesity (Dermum's disease?), etc.
 3. Physiological (old age).
- V. Regeneration (hyperplasia).

- VI. Degeneration.
 - 1. Hyaline.
 - 2. Calcareous.
 - 3. Amyloid, etc.
- VII. Inflammations.
- VIII. Tumors.
 - 1. Benign.
 - (a) Fetal adenoma.
 - (b) Simple adenoma.
 - 2. Malignant.
 - (a) Carcinoma.
 - (i) Originating from fetal adenoma.
 - (ii) Glandular carcinoma.
 - (b) Sarcoma.
 - (c) Endothelioma, etc.
- IX. Complications.
 - 1. Hemorrhage and its sequelæ.
 - 2. Cysts, etc.

This general outline or skeleton of the major types of changes occurring in the thyroid differs somewhat from the usual ones of text-books in several important particulars. First and most important perhaps is that colloid glands have been removed from the group of degenerations and placed on the same plane with normal glands and the hyperplasias. This was the result of both an anatomical and experimental study.²

Second, it indicates the sequence of changes occurring in the gland, e. g., colloid glands are placed after the active hyperplasias because it has been shown that all colloid glands have at one or more times been in the stage of active hyperplasia.

Likewise atrophies, apart from the physiological (senile) form, are in all probability always preceded by a greater or lesser degree of active hyperplasia.³

In the present communication we are concerned only with normal actively hyperplastic and colloid glands, inasmuch as these are the only fundamental types concerned in the production of true goiter. Certain relations with the remaining groups of the general schema will, however, be pointed out in their proper places.

The anatomical descriptions to follow will, in the main, be confined to the human thyroid, inasmuch as extended descriptions of similar changes in other animals have already appeared.⁴

2. Von Bruns: *Beitr. z. klin. Chir.*, 1896, xvi, 521. Marine and Lenhart: *Johns Hopkins Hosp. Bull.*, 1909, xx, 131.

3. Ord, W. M.: *Brit. Med. Jour.*, 1898, ii, 1473. Howard, C. P.: *Myxedema. Jour. Am. Med. Assn.*, 1907, xlviii, 1325.

4. Marine: *Cleveland Med. Jour.*, 1907, vi, 45. Marine: *Johns Hopkins Hosp. Bull.*, 1907, xviii, 359. Marine and Williams: *The relation of iodine to the structure of the thyroid gland. THE ARCHIVES INT. MED.*, 1908, i, 349.

I. NORMAL THYROID*

The normal human thyroid⁵ differs histologically in no essential way from similar glands in the dog, sheep, ox, pig or horse. In the past histologists have differed somewhat as to the characteristics of normal glands, but these differences were dependent largely on the regional and accidental circumstances of the material used. The more recent descriptions given by Müller,⁶ Bozzi,⁷ and Ebner⁸ show a general agreement. From these authors' descriptions, however, it can be seen that no sharply cut, terse description of the histology is universally accepted. This is to be expected in regard to a gland like the thyroid, which reacts so quickly to the many changes and alterations in the body metabolism. It was pointed out by Hale White⁹ that if one examined any large series of human thyroids he would find great variations in the histological appearance in subjects that, during life, showed no manifestations of diseases known to be associated with thyroid changes. This observation has been confirmed by all subsequent observers.

The perfectly normal, adult thyroid weighs between 20 and 30 gm. This is lower than the weight usually stated (30 to 40) and applies to the seacoast type, for there is no doubt that in goitrous districts much larger glands are considered normal, although from our observations we believe that all such glands have at one time or another shown hypertrophic changes, and if histologic examination shows any evidence to that effect we class them as colloid glands.

The lateral lobes are in general symmetrical and of uniform size, though slight variations are not infrequent. So also with the isthmus and pyramidal portion. The outer fibrous areolar capsule is thin and strips easily, leaving a slightly lobulated smooth surface. The capsule proper is thin and translucent, and thickened portions (trabeculæ) extend into the gland, mark out the lobules, and support the blood and lymph vessels. The general color varies from a pale amber red to a

* See Figure 1.

5. The parathyroid glands have been examined in all autopsy specimens and it may be stated that we have found them remarkably constant in number and position when one considers their normal number (four) and their size. They usually partake of the color of the thyroid, i. e., are pale yellow in the lighter red and brown yellow in the darker red thyroids. We have seen no evidence suggesting that they react anatomically with the thyroid in its goitrous changes and we believe that they are quite independent structures.

6. Müller, L. R.: *Beitr. z. path. Anat. u. allg. Path.*, 1896, xix, 127.

7. Bozzi: *Beitr. z. path. Anat. u. allg. Path.*, 1895, xviii, 125.

8. Ebner: *Koelliker's Handbuch der Gewebelehre des Menschen*. Leipzig, 1899, iii, 316.

9. White, Hale: *Med. Chir. Tr.*, 1888, lxxi, 181.

bright amber red. On section the follicles can just be distinguished with the naked eye and vary greatly in diameter (0.3 to 0.5 mm.). They are filled with a clear amber-yellow viscid colloid.

Microscopically the follicles are in general round or oval closed spaces of somewhat irregular size. They are lined with a single layer of flat cubical or, at most, cubical epithelium (high cubical or columnar types of epithelium always indicate hypertrophy). The cells are quite regular in size and in certain specimens the so-called "chief" and "colloid" cells described by Langendorf¹⁰ can be made out. These changes probably represent different secretory activities of the cells. The nuclei are small, basal, darkly staining and vesicular. The colloid lies in contact with the free border of the epithelial cells. It is homogeneous and stains deeply with cosin. The colloid of adjacent follicles may not stain with the same intensity, and colloid-like material is frequently to be seen in the lymphatic spaces—an observation usually taken as evidence that the lymphatics form the normal paths of exit for the colloid.¹¹ The blood and lymph vessels, though forming rich networks about the follicles, are not prominent, nor are the larger vessels of the trabeculae and capsule thick-walled and tortuous as in the colloid goiters.

II. ACTIVE THYROID HYPERPLASIAS*

There is no essential difference between the forms seen in human and those seen in dog, sheep, ox or pig thyroids. Pure types of hyperplasia are, of course, less frequently observed in man. Detailed descriptions of these changes in the dog, sheep and ox have already appeared and it remains only to outline those occurring in the human thyroid. Active hyperplasias, being the first or primary phase of goiter formation, are most frequently observed in the goiter-developing epochs—namely, childhood, puberty and pregnancy—although a great many thyroids show active hyperplasia when there is no clinical evidence of thyroid abnormality. The classical and perhaps best known example of thyroid hyperplasia in man occurs in exophthalmic goiter.

In man, just as in the lower animals, one observes all degrees of hyperplasia, from the very slightest changes from normal or colloid glands (hypertrophy) to the most marked epithelial proliferation (hyperplasia).

10. Langendorf: *Biol. Centralb.*, 1889-90, ix, 426.

11. Baber: *Quart. Jour. Micr. Sc.*, 1877, new series, xvii, 204. Hürthle: *Arch. f. d. ges. Physiol. (Pflüger's)*, 1894, lvi, 1. Zeiss: *Inaug. Diss. Strassburg*, 1877.

* See Figures 2, 3, 4, 5, 6.

As has been discussed at some length in other publications (Marine and Williams⁴ and Marine and Lenhart²), it is necessary to recognize two series of hyperplasias—(1) normal (2), colloid. The normal series includes all cases of hyperplasia which are engrafted on normal glands and the colloid series of hyperplasias include all cases in which the hyperplasias are engrafted on colloid glands. This secondary hyperplasia (secondary in the sense that it is not the first time these glands have undergone active hyperplasia) is well recognized in human goiter, especially as the so-called “secondary exophthalmic goiter,” and of late we have recognized that secondary hyperplasia occurs in colloid glands just as readily as primary hyperplasia occurs in normal glands, and as a result of the same causes, either with or without (usually without) the clinical signs of exophthalmic goiter. Since the conditions favorable to the development of colloid glands (variations in food, body nutrition, locality, etc.) more commonly affect man and dog, colloid glands and the several degrees of the colloid series of hyperplasias are more often seen in these animals.

For convenience of description and of analysis we have divided the two series (normal and colloid) into subgroups, as follows: (1) *Normal-early, early, early-moderate, moderate, moderate-marked and marked glandular hyperplasia*; (2) *colloid-early, colloid-early-moderate, colloid-moderate, colloid-moderate-marked and colloid-marked*.

The early stages of hyperplasia are the most important, for the reason that the first change from the normal gland marks the first step in the formation of goiter, and it is now generally recognized that the primary phase of all true goiters is active hyperplasia (Virchow¹).

Tracing the process of hyperplasia, the first change noted in the thyroid is an increased blood supply to the gland. The capsular vessels are dilated. They become tortuous. The capillaries surrounding the follicles are dilated and congested. The gland becomes larger and softer and takes on a brighter red color. Microscopically there is lessening of the stainable colloid; at first but palely staining, later vacuolization, and finally actual disappearance of the true colloid—its place being taken by a glandular albuminous debris in which are seen leucocytes and shed epithelial cells.

The flat-cubical or cubical epithelial cells of the normal or colloid glands at first become high cubical with larger and more vesicular nuclei; later they become columnar, and finally high columnar. Then, as hyperplasia takes place, infoldings and plications of the lining epithelium are formed. This process is apparently an attempt to increase the epithelial surface without undue general glandular enlargement. The connective-

tissue framework of the capsule and trabeculæ increases. This is at first probably only a compensatory process to support the great increase of epithelial elements and the increased blood supply.

The now well-recognized and clear descriptions of the essential histological changes in exophthalmic goiter, which have been developed by Bramwell,¹² Greenfield,¹³ Edmunds,¹⁴ Farner,¹⁵ Von Hansemann,¹⁶ Hirschlaff,¹⁷ Mac Callum,¹⁸ Ewing,¹⁹ Lewis,²⁰ Wilson,²¹ and others, represent the most familiar type of extensive active hyperplasia in man, but by no means the most frequent one, since identical histological changes are observed in the prenatal, puberty and pregnancy thyroid enlargements. To sum up: The thyroid changes in all forms of active hyperplasia are characterized by an increase in the blood supply and the lymphatic drainage; a decrease in the stainable colloid; marked hypertrophy and hyperplasia of the follicular epithelium; a variable increase in the stroma, and frequently deposits of lymphoid tissue here and there throughout the stroma.

In addition to the necessity of establishing two series of hyperplasias—normal and colloid, as above mentioned—and the ready explanation it affords in many histological pictures of hyperplasia, there is perhaps another factor that modifies our interpretation of hyperplasias which has not been sufficiently emphasized in the published descriptions. It is the occurrence of atrophic changes. This type of atrophy seems to differ from simple cell atrophy in that there is a marked disturbance in the nucleus-plasma relationship, and, as it has been observed only in glands with marked hyperplasia from subjects that during life showed clinical signs of myxedema or cretinism, its significance will be discussed along with these diseases.

III. COLLOID GLANDS*

The third great natural division of thyroid changes are the colloid glands (goiters). In our human series it will be noticed (see Tables 8 and 1) that there are 25 colloid glands and 23 normal. This surprising proportion of colloid glands is due to two factors. First, in goitrous

12. Bramwell: *Atlas of Clinical Medicine*, Edinburgh, 1892-3, ii, 91.

13. Greenfield: *Brit. Med. Jour.*, 1893, ii, 1261.

14. Edmunds: *Lancet*, London, 1901, i, 1317, 1381, 1449.

15. Farner: *Virchow's Arch. f. path. Anat.*, 1896, cxliii, 509.

16. Von Hansemann: *Berl. klin. Wehnschr.*, 1905, No. 44a 65.

17. Hirschlaff: *Ztschr. f. klin. Med.*, 1899, xxxvi, 200.

18. MacCallum: *Johns Hopkins Hosp. Bull.*, 1905, xvi, 287.

19. Ewing: *Tr. Assn. Am. Phys.*, 1906, xxi, 567.

20. Lewis: *Surg., Gyn. and Obst.*, 1906, iii, 476.

21. Wilson: *Am. Jour. Med. Sci.*, 1908, cxxxvi, 851.

* See Figure 7.

districts hyperplasias are much more common than normal glands (the proportions of hyperplasia to normal in our normal series' collection being 53 to 3 for dogs, 14 to 19 for sheep, 6 to 18 for pigs, 20 to 17 for cattle and 23 to 23 for man) and all reverted hyperplasias are colloid glands (goiters). Second, we have called all glands colloid that show any evidence of having previously undergone active hyperplasia. Thus there are many glands that, as regards size, shape, color, consistency, colloid and histological appearance, would ordinarily be considered normal. They are physiologically normal, but they show the marks of a previous hyperplasia, and for sake of strict anatomical analysis it is necessary to recognize these anatomical differences.

Pure colloid glands (goiters) present no essential differences in any of the animals examined. They differ essentially from normal glands in all these animals only in size (though, as has just been pointed out, they may be no larger than normal) and in showing the vestiges of previous hyperplasia. These marks of previous hyperplasia, however, are well-defined and characteristic. Their prominence in any given specimen depends on the degree and duration of hyperplasia and the length of time since the reversion occurred. These changes are to be found in the size and shape of the follicles, in the presence of sprig-like projections into the follicles in the more recent involutions (reversions), in the blood and lymph vessels, and in the stroma and capsule. The epithelium is normal (flat cubical), the stroma is increased, although to this statement there are exceptions depending on the extent of the fibrosis occurring during the active hyperplasia and the extent of the absorption which normally occurs during the process of reversion. Thus we have seen markedly cretinoid pups' thyroids, in which the stroma was so increased that the scattered thyroid follicles gave the gland the appearance of the endometrium, so resolve in the course of a month following the administration of iodine as to have all the appearances of a pure colloid gland with normal stroma. Such cases illustrate how rapidly the body can adjust physiological defects. The thickened thyroid capsule is likewise the inheritance from the preceding hyperplasia and varies greatly in thickness in different specimens. The arterial walls are always thickened and histologically show an obliterating endarteritis similar to that seen in the involuting thymus or uterus. Calcification is very common in these thickened walls, and even the veins may contain calcareous deposits in their walls. The most striking change in the veins and lymphatic trunks is the great lessening in their caliber. This is associated with some thickening of their walls. The stainable colloid is normal in appearance and distribution in the follicles. The follicles are in general

much larger than in normal glands, but this depends on the degree of hyperplasia preceding the involution (reversion), and perhaps also on other as yet ill-defined factors, as, for example, the cause of reversion and the duration of the process. If only a hypertrophy has preceded the involution (reversion), then it is scarcely possible to distinguish such a gland from normal. We have met several glands of which we could neither convince ourselves that the structure was normal nor offer definite proof of a previous hyperplasia. These glands we have called "normal-colloid" and have separated them for analytic purposes. The sprig-like projections into the follicles are the remnants of the infoldings or plications occurring during the preceding hyperplasia and there is evidence that these sprigs are slowly effaced in long-standing colloid glands (goiters).

Only brief mention in the way of explanation of the other divisions of the classification can be made here, inasmuch as they are not primarily concerned in the production of goiter and will be discussed in a later publication.

IV. ATROPHY

Atrophy is a normal senile process. The thyroid is most active in youth, as is also goiter formation. True goiter rarely develops after 45 years of age.²² Simple atrophy also occurs in many of the chronic diseases, and is particularly associated with chronic pulmonary tuberculosis. The special forms of atrophy leading to colloid glands, and consequent upon the hypertrophies and hyperplasias of puberty, menstruation and pregnancy, are best considered involutions (reversions).

The form associated clinically with the symptom-complex of myxedema, first recognized by Gull²³ and later carefully described by Ord²⁴ and Hun and Prudden,²⁵ is of particular interest in that it is a form of atrophy occurring in spite of attempts at hyperplasia and is apparently the result of sustained thyroid stimulation without intervening periods of physiological rest. It is coming to be more recognized that this form of atrophy is practically always preceded by hyperplasia, with or without the symptom-complex of exophthalmic goiter. This change is seen particularly in cases of exophthalmic goiter that are passing over into myxedema. Briefly, the histological changes are as follows: The epithelial cells lose the regular and uniform type characteristic of the usual hyperplasia and become irregular in size and shape. There is desquama-

22. Horsley: Brit. Med. Jour., 1892, i, 215.

23. Gull: Tr. Clin. Soc., London, 1874, vii, 180.

24. Ord: Med.-Chir. Tr., London, 1878, lxi, 57.

25. Hun and Prudden: Am. Jour. Med. Sc., 1888, xcvi, 140.

tion and piling up of the epithelial cells in the vesicles. The nuclei are in general enlarged, hyperchromatic and irregular in size and shape. Nuclear figures are observed, but the new formation of cells is not sufficient to offset the cell degeneration and the vesicles become smaller. The surrounding fibrous tissue is relatively, perhaps absolutely, increased, and, as the vesicles are reduced in size, they are more and more widely separated. The interstitial cirrhosis, we believe, is secondary and consequent on the destruction of the epithelial elements. We have frequently observed the milder forms of this type of atrophy in exophthalmic goiter thyroids and feel sure that it is more common than the literature reports indicate.

V. REGENERATION

Except for normal replacing of cells as they die—a process which is continually going on in most glandular tissues—regeneration is a compensatory process and hence is more aptly considered a part of the general group of hyperplasias. Regeneration occurs following partial destruction or removal of the thyroid, as has been amply shown for man and animals.²⁶

The new-formed tissue may remain normal in structure, as occurs in young animals after partial removal with the administration of iodine, or it may take on the characteristics of true spontaneous hyperplasia, as in similar cases of partial removal without the administration of iodine. The two groups of "Regeneration" and "Hyperplasia" are so nearly a part of each other that it is impossible to distinguish sharply between them. To say that regeneration stops when the thyroid tissue has attained its normal amount is not in accord with all the known facts. The normal gland shows considerable variation in different subjects and, besides, there are at least two factors concerned: the first is the actual number of cells necessary to perform the thyroid functions under favorable conditions of nutrition and metabolism, and the second factor is the degree of cell proliferation which may occur in conditions of malnutrition or disturbed nutrition. Thus the statement sometimes made that compensatory regeneration does not exceed the normal size of the gland²⁷ is not in accord with our present knowledge, for the reason that the extent of the cell proliferation in the thyroid depends on the physiological

26. Wagner: *Wien. med. Bl.*, 1884, vii, 771. Schiff: *Arch. f. exper. Path. u. Pharmakol.*, 1884, xviii, 25. Halsted: *Johns Hopkins Hosp. Rep.*, 1896, i, 373. Welch: *Med. Rec.*, New York, 1888, xxxiv, 368. Horsley: *Brit. Med. Jour.*, 1892, i, 215. Ribbert: *Virchow's Arch. f. path. Anat.*, 1889, cxvii, 151. Sulzer: *Ztschr. f. Chir.*, 1893, 191.

27. MacCallum, W. G.: The pathology of exophthalmic goiter. *Jour. Am. Med. Assn.*, 1907, xlix, 1158.

requirements of the animal and this can be markedly influenced by diet, iodin, etc.

VI. DEGENERATIONS

Degenerations include calcareous, hyaline and amyloid changes and are never seen apart from other pathological processes, as hemorrhage, cyst formation, etc. These changes are very frequently seen in old colloid goiters, but they are always secondary changes and are never essential parts of the colloid transformation. Pure colloid goiters are not degenerative processes, as they have long been considered. They are more allied to the atrophies and are, properly speaking, involutions, since it is now definitely known that they obey all the known biological laws of normal glands (Marine and Lenhart²).

VII. INFLAMMATIONS

Apart from a general view that all goiter is inflammatory in nature, true inflammations as we regard them to-day are rare.²⁸ They may, however, occur in the course of many of the infectious diseases, as lues, tuberculosis, typhoid, influenza, etc. Inflammation has frequently followed injuries, as in the old treatment of goiter by iodin and iron injections.²⁹

VIII. TUMORS

The most frequent tumor of the thyroid is the fetal adenoma, as described by Billroth,³⁰ Bloodgood,³¹ and others. These are usually small, frequently multiple and may attain the size of one's fist. There are apparently several types or phases of these tumors, ranging from the type closely resembling fetal thyroid which gave rise to the name, to the well-differentiated colloid-containing form. Likewise these tumors are known to undergo (reversion) involution to the colloid or quiescent state, in which they can not be differentiated from ordinary colloid goiter except for the smaller size of the alveoli and their complete encapsulation.

Aside from the above-described form one finds encapsulated adenomatous growths of well-differentiated thyroid tissue growing, in some instances, apparently independently of the rest of the thyroid gland and histologically resembling the well-differentiated cells of ordinary thyroid hyperplasia. Without any definite evidence, we are inclined to look on them as closely related to the fetal adenoma, being only a fully differentiated type.

28. Ewald, C.: München. med. Wehnschr., 1896, xliii, 634.

29. Semon: Brit. Med. Jour., 1885, i, 715.

30. Billroth: Arch. f. Anat. Physiol. u. wissenschaft. Med., Berlin, 1856, 144.

31. Bloodgood: Surg., Gyn. and Obst., 1906, ii, 121.

Carcinoma of the thyroid is difficult of diagnosis microscopically. It has long been known that not infrequently one finds apparently benign types of thyroid tumor in what are undoubtedly metastases, and also there are cases reported in which metastatic thyroid tissue has been found with no evidence of a primary growth in the thyroid. Thus it is probable that we have not recognized some of these tumors, but, on the other hand, it is probable that there are tumors reported as carcinoma that are not. In our experience, however, carcinoma of the thyroid in man is rare. It would appear to be in some way related to the frequency of goiter, and even associated with goiter itself. Pick,³² working with the carcinoma of brook trout, was inclined to such a view. We have observed two types of thyroid carcinoma. One, histologically, closely resembles the fetal adenoma tissue and might be called malignant fetal adenoma. The other preserves the characteristics of differentiated thyroid tissue. Seven cases of carcinoma of the thyroid in old dogs have come to our notice. Three of the cases had lung metastases. In all there had been long-standing goiters. In none was there accompanying sarcoma, as has been reported by Schöne.³³ The epithelial changes were similar to those described by the above observer.

We have seen one case of lymphangioendothelioma probably originating in the thyroid, but no case of true sarcoma.

IX. COMPLICATIONS

Hemorrhage and its sequelæ are the most frequent secondary changes in goiter. Hemorrhage occurs more commonly in the colloid phase. It is dependent on trauma and overdistention of the alveoli with subsequent rupture of their walls.³⁴ Hemorrhages occur in all animals in which colloid glands are seen and their relative natural frequency probably is the same, although it seems more common in dogs. Trauma, as in fighting and sudden violent exertions causing venous engorgement, perhaps plays an important rôle in dogs. Cysts are the most important sequels of hemorrhages and we are inclined to believe with Bradley³⁵ that the great variety of cysts seen in the thyroid are probably primarily of hemorrhagic origin. Occasionally small hemorrhages are seen in otherwise histologically normal glands. Hydatid cysts are occasionally reported.

It seems clear from the preceding anatomical discussion that in the development of the true goiter only three groups are primarily involved—viz.: (1) normal glands, (2) hyperplasias, and (3) colloid glands. The

32. Pick: Berl. klin. Wehnschr., 1905, xlii, 1536.

33. Schöne: Virchow's Arch. f. path. Anat., 1909, cxcv, 169.

34. Wölfler: Arch. f. klin. Chir., 1883, xxix, i, 754.

35. Bradley: Jour. Exper. Med., 1896, i, 401.

variety of secondary and complicating changes, as atrophy, degeneration, regeneration, cyst formation, etc., is almost infinite. Of the three great groups, normal glands are the most important to have firmly established, since they form the base to which all other changes must be referred for comparison.

Active hyperplasias comprise a gradation from the nearly normal or colloid gland (true hypertrophy) to the extreme degrees of hyperplasia seen in exophthalmic goiter. The histological appearance of a given specimen, apart from the degree of hyperplasia and whatever secondary changes may be present, is modified by two important factors—viz: (1) the number of times the gland has returned to the colloid state (reversion), as, for example, in the case of repeated pregnancies when during each pregnancy there was active hyperplasia and during each interval there was a return to the colloid state; and (2) the length of time active hyperplasia has continued without a period of rest. Thus, in the marked hyperplasias of exophthalmic goiter or of cretins,³⁶ we see apparent overgrowth of fibrous tissue with very striking irregularities and disturbances in the nucleus-plasma relations of epithelial cells. These nucleus-plasma disturbances in cretin dogs are able to right themselves when iodine is administered, and in such glands one may then produce a regular, uniform, compensatory hyperplasia by partial removal. Colloid glands are but exaggerations of all the structures of normal glands, depending on the degree of active hyperplasia preceding the involution (reversion). It is our belief that all colloid glands have been preceded by active hyperplasia, and that passive dilatation of the alveoli due to continued secretory activity and obstruction to the lymphatic drainage is of secondary importance. Rupture of the alveoli and other secondary and complicating changes may occur. So also a colloid gland may undergo secondary active hyperplasia differing essentially in no way from the primary form occurring in a normal gland.

RELATION OF SEX AND AGE OF THE ANIMAL AND SIZE OF THE GLAND TO HISTOLOGIC STRUCTURE

It is usually stated by anatomists that the normal human thyroid is larger in infants and children and in females than in later periods of life or in males—i. e., larger in relation to the body weight. Other than this, sex and age have no particular relation to normal glands. The normal gland at birth is well differentiated into colloid-containing vesicles in the sheep, dog, ox and man. As a class normal glands are the

36. McGarrison: Proc. Roy. Soc. Med., 1908, ii, No. 3, Med. Section, p. 1.

smallest met. The average weights in our series were 2.08 gm. for dogs, 12 gm. for oxen, 6.9 gm. for sheep, and 24 gm. for man.³⁷

Active hyperplasias in man are definitely associated with age and sex. Sex has no important relation to the hyperplasias in the dog, ox, sheep and pig. In man also sex is not a modifying factor in the hyperplasias of infancy and childhood. Starting with puberty, however, active hyperplasia is more common in females. The clinical incidence is variously estimated³⁸ from 3 to 1 to 6 to 1. The actual or anatomical incidence in our series is modified by the larger proportion of males in the autopsy material and the larger proportion of females in the surgical material; and also by the fact that any thyroids showing anatomical complications were not used. These factors make deductions worthless. The metabolic disturbances associated with the establishment of menstrual functions, with menstruation, with pregnancy and lactation, and with the menopause are particularly associated with goiter development. Nothing is known definitely regarding the physiological nature of the disturbances which stimulate the thyroid to hyperplasia at these particular periods.

Age is a factor in the hyperplasias common to all animals. They are more frequently observed in the young, when the thyroid is normally functionally more active. This is particularly true of the lower animals. In man it is also true, but there are modifying factors not sufficiently prominent in the lower animals, as, for example, the sexual cycle and the disturbances leading to exophthalmic goiter, which are particularly associated with goiter formation, and which modify the age limitations of human goiter.

As regards the size of the glands, it may be stated that the size varies with the degree of hyperplasia. There are exceptions to this rule, especially in man. These exceptions most likely depend on a more complicated etiology and life cycle in human goiters..

Colloid glands of the lower animals have no noteworthy relation to sex. Sex is also not a factor in human colloid glands before puberty. After puberty colloid glands are more common in females, for the reason that hyperplasias are more common.

Age is a very important factor in colloid glands of all animals. They are always sequels of active hyperplasia and therefore occur at correspondingly later periods of life. The size of the colloid gland depends mainly on the degree of hyperplasia preceding the involution (reversion). Other factors, as repeated hyperplasia, medication and lymphatic obstruc-

37. Wondenberg (Virchow's Arch. f. path. Anat., 1909, cxvii, 107) has reported much higher weights for normal glands in these animals.

38. Dock: Osler's Modern Medicine, 1909, vi, 404.

tion inducing passive dilatation of the vesicles, operate, to a less extent, to modify the size. Thus colloid glands may be no larger than normal glands, or they may attain the size of the largest goiters.

Summing up, it is seen that age and sex bear no important relation to normal glands. In the hyperplasias age is of great importance, while sex is an important factor only in those hyperplasias in man occurring during and after puberty. In colloid glands age is also a very important factor in all animals—while sex is important in the human forms occurring during and after puberty.

As regards size, normal glands as a class are the smallest observed. In the hyperplasias the size depends on the degree of hyperplasia and in colloid glands the size as a rule depends on the degree of the preceding hyperplasia. Thus, while the size of the gland, the age and the sex of the animal are related to the gland structure and its variations, they can be considered as only secondary and accompanying factors to the fundamental causes in the etiology of goiter.

IODIN DETERMINATION

Iodin determinations have been made on 161 different human thyroids, of which 96 are used in the following 14 tables, where they have been classified according to their histology. The method used in determining the iodine content is fully described in an earlier publication (Marine and Williams⁴) and has been used throughout without modification. We have used several modifications of the method proposed from time to time, but all our observations by means of these modifications and of controls in thirty-one cases have convinced us that the above method will not lead to erroneous conclusions if only the iodine content in relationship with the histological structures is considered. The method and the proposed modifications are not quantitatively accurate.

The three natural anatomical groups—viz: (1) normal thyroids, (2) colloid thyroids, and (3) actively hyperplastic thyroids, with the arbitrary subdivision of the latter group—are also the same as those previously used and described.

The anatomical standards being the same or as nearly the same as it was possible to make them, we have also brought forward the iodine determinations in dog, sheep, pig and ox thyroids for comparison.

One important addition to the earlier recorded observations will be noted in that the human colloid series is nearly complete and the canine colloid series is sufficiently complete to parallel the normal series in these two animals and will be discussed with equal emphasis.

The reasons—*anatomical, chemical (iodin) and biological*—for establishing a colloid series parallel with the normal series have already been set forth at some length (Marine and Lenhart²) and need not be reviewed here except to state that the only essential difference between normal and colloid glands is that colloid glands have at some time undergone active hyperplasia, while strictly normal glands have never undergone such hyperplasia.

As above stated, 161 different human thyroids have been analyzed for iodine, of which 111 were autopsy specimens and 50 surgical specimens. Of these only 96, of which 77 were autopsy specimens and 19 surgical specimens, have been included in the tables of analysis. Of the 34 (30.6 per cent.) autopsy specimens not used 11 were from children under two years; 10 from old subjects showing histologically marked senile atrophy; 2 contained multiple small fetal adenomata; 3 showed marked atrophy with fibrosis associated with chronic pulmonary tuberculosis; 6 had, to our knowledge, been fed large amounts of iodine-containing compounds during the last few months of life; 1 showed marked simple atrophy without assignable cause (myxedema), and 1 specimen had been handled for demonstration purposes. Of the 31 (62 per cent.) surgical specimens not used, 11 had been previously treated with iodine containing compounds; 14 were discarded on account of old hemorrhagic-cystic-degenerative changes; 5 were discarded on account of fetal adenomata, and 1 for malignant tumor (endothelioma).

The fact that 65 (40.4 per cent.) could not, for one or another reason above mentioned, be included in the tables clearly shows that no conclusions can be drawn from a limited material even if this material be from autopsies with no clinical suspicion of thyroid disease. With surgical material this is especially true. Our percentage (38 per cent.) of uncomplicated surgical specimens is unusually high and is due to the presence of several uncomplicated cases of exophthalmic goiter. We have pointed this out specifically here because in all publications thus far recorded on the relation of iodine to human goiter the complicating factors have not been taken into account. We also feel certain that a larger series than we have here recorded, whether autopsy or surgical, would modify the figures here given, particularly if the district from whence the glands were taken were goitrous, while, on the other hand, a smaller series would give more uniform results if seacoast glands were used.

Pure types of histological changes only can be used, because, in the present state of our knowledge, we can not discount for the multiple anatomical complicating factors so common in the thyroid and which have already been alluded to.

Then, too, besides the anatomical complications, there are a great group of metabolic (physiological) changes producing effects on the structure or secretion of the gland either too slight or too temporary to be accurately ascertained or discounted. We refer to such conditions as variations depending on the seasons of the year,³⁹ on the sexual functions, on rest, on menstruation, on pregnancy, on climatic variations,⁴⁰ on food variations, etc.

Thus by eliminating all known untoward factors there are still present many uncertainties which can not be avoided at present and render conclusions from such data dangerous except those on the general relation of iodine with the structure and physiology of the thyroid.

The individual cases of the normal and colloid human series have been tabulated separately (Tables 15 and 16). It will be noticed that in only a few cases is the iodine content calculated for the fresh gland. This is due to the fact that the other specimens had been preserved in 10 per cent. formalin from one to seven days before being used. This factor, as Williams⁴¹ has shown, makes little or no difference as regards the iodine content per gm. of dried gland.

It was impossible to get actual weights of the thyroids in the fresh condition in most instances and we have only indicated roughly their size by the terms "normal," "slightly enlarged," "moderately enlarged" and "markedly enlarged." Thus thyroids from adults weighing between 20-30 gm. we have called "normal," between 30 and 50 "slightly enlarged," between 50 and 100 "moderately enlarged," and over 100 gm. "markedly enlarged."

Since the iodine content in relationship with the individual anatomical groupings has been discussed at length in earlier publications, they will here be discussed collectively in relationship with the basic anatomical groups—normals, colloids and the two series of hyperplasias.

NORMAL GLANDS *

Normal glands have the highest mean and average iodine content per gram. This is true for all animals thus far examined. In our twenty-three human specimens the highest iodine content per gram of dried gland was 3,691 mgm.; the lowest 1,307 mgm. The significance and explanation of this great variation in histologically normal glands becomes of

39. Koch, F. C.: Discussion on Hunt and Seidell's paper on commercial preparations. *Jour. Am. Med. Assn.*, 1908, li, 1389.

40. Sawyer, J. P.: *New York Med. Jour.*, 1907, lxxxvi, 68.

41. Marine, D., and Williams, W. W.: The relation of iodine to the structure of the thyroid gland. *THE ARCHIVES INT. MED.*, 1908, i, 378.

* See Tables 1 and 15.

greater importance when one notes that it is also seen with the dog, sheep, ox and pig thyroids. Whether it indicates variations in the intake or variations in the consumption within the organism, or both, is not clear. The evidence at present available indicates that the consumption of iodized protein in the body is the most constant. Thus it is known that the administration of very small amounts of iodine is followed by its rapid storage in the gland in all animals, the rapidity of the process depending on the degree of hyperplasia (therefore, on the lack of iodine). On the other hand, it is known that the withholding of iodine, as by a fresh meat diet,⁴² causes a slow loss of iodine from the gland. That these variations (1.307-3.691 mgm.) are not due to accumulation of iodine, either by accident or to an effort to render inert the poisonous properties of iodine, is both true and false. Thus there are differences that depend purely on the accidental content of the food in iodine. It is also probably true that the iodine, so long as it remains in the thyroid, is inert (to the host), because it represents merely the stored iodine, or the factor of safety. On the other hand, broadly interpreted, none of the iodine in the thyroid is inert or accidental, inasmuch as it is stored there for the purpose of later becoming available to the organism. All observers, from whatever angle they approach the question, have concluded that the iodine content determined the physiological activity of the protein (thyroglobulin). Thus Roos⁴³ observed that the increased nitrogen excretion induced by feeding thyroglobulin depended on its iodine content. Hunt⁴⁴ has found that the protection offered to mice against acetonitrile poisoning depends on the iodine content. We have shown the biological fact that if the iodine falls below a quite constant level the gland undergoes characteristic and constant histologic changes, while, if iodine is given, these changes either do not occur or, if they have started, they are arrested. As one of us⁴⁵ has previously indicated, we believe that the organism retains iodine in the same way that it retains iron and calcium, etc., and that the difference between the greatest amount of either iodine, iron or calcium and the least amount that may be found in the animal to be compatible with the maintenance of normal histological structure of the tissues immediately concerned with their storage and elaboration, represents the excess of intake over consumption, or the true physiological factor of safety.⁴⁶

42. Baumann: München. med. Wchnschr., 1896, xliii, 309.

43. Roos: Ztschr. f. physiol. Chem., 1899, xxviii, 40.

44. Hunt: The relation of iodine to the thyroid gland. Jour. Am. Med. Assn., 1907, xlix, 1323.

45. Johns Hopkins Hosp. Bull., 1907, xviii, 359.

46. Meltzer, S. J.: The Harvey Lectures, 1906-07. Lippincott, Philadelphia, 1908, p. 139.

NORMAL SERIES—VARIOUS ANIMALS

TABLE 1.—NORMAL GLANDS *

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep	19	4.614	2.288	2.467	1.318	0.694	0.686
		1.247			0.318		
Dog	3	4.722	3.205	3.322	1.064	0.757	0.777
		1.990			0.512		
Pig	18	4.153	2.412	2.515	1.456	0.778	0.884
		1.538			0.425		
Ox	17	4.768	3.254	3.461	1.592	1.069	1.117
		2.730			0.892		
Man	23	3.691	2.153	2.171	0.451	0.403	0.402
		1.307			0.310		

* In this and the following tables, E stands for extreme, M for mean, and A for average. Iodin figures are in mgm.

TABLE 2.—NORMAL-EARLY GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep	1	0.677	0.176
			
Dog	7	1.296	0.815	0.879	0.318	0.153	0.174
		0.483			0.018		
Pig	1	1.230	0.337
			
Ox	7	2.676	2.307	2.317	0.726	0.653	0.628
		2.000			0.482		
Man	4	0.984	0.807	0.803	0.216	0.206
		0.615			0.196		

TABLE 3.—EARLY GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep
			
Dog	9	1.028	0.654	0.625	0.235	0.113	0.139
		0.243			0.063		
Pig	2	1.158	1.102	0.291	0.285
		1.046			0.279		
Ox	3	2.186	1.630	1.646	0.615	0.456	0.462
		1.123			0.314		
Man	5	1.077	0.877	0.895
		0.738				

TABLE 4.—EARLY-MODERATE GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep	1	0.548	0.131
		
Dog	1	0.262	0.082
		
Pig	3	0.846	0.769	0.795	0.241	0.233	0.224
		0.769			0.198		
Ox	5	1.030	1.000	1.000	0.252	0.222	0.226
		0.969			0.205		
Man	3	0.738	0.554	0.566
		0.406			

TABLE 5.—MODERATE GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep	1	0.400	0.091
		
Dog	9	0.854	0.345	0.368	0.136	0.076	0.078
		0.101			0.026		
Pig
		
Ox
		
Man	2	0.807		0.711
		0.615	

TABLE 6.—MODERATE-MARKED GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep	5	0.092	0.024	0.031	0.014	0.003	0.004
		0.000			0.000		
Dog	9	0.660	0.231	0.283	0.109	0.042	0.055
		0.058			0.011		
Pig
		
Ox
		
Man	2	0.480		0.406
		0.332	

TABLE 7.—MARKED GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep	6	0.036			0.006		
		0.000	0.000	0.006	0.000	0.000	0.001
Dog	18	0.640			0.123		
		0.008	0.073	0.114	0.002	0.014	0.023
Pig
	
Ox	5	0.270			0.062		
		0.077	0.215	0.189	0.016	0.042	0.041
Man	7	0.584			0.115		
		0.118	0.292	0.323	0.060	0.109	0.095

COLLOID SERIES—VARIOUS ANIMALS

TABLE 8.—COLLOID GLANDS

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep	3	3.691			1.027		
		1.769	3.529	2.996	0.455	0.974	0.818
Dog	8	3.608			1.039		
		0.846	1.816	1.985	0.132	0.406	0.459
Pig	2	2.768			0.805		
		1.938	2.353	0.557	0.681
Ox
	
Man	25	3.914			0.798		
		0.784	1.769	1.996	0.304	0.479	0.515

TABLE 9.—COLLOID-EARLY GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep	4	1.000			0.282		
		0.461	0.853	0.792	0.138	0.201	0.206
Dog	6	1.443			0.302		
		0.431	0.953	0.945	0.125	0.221	0.217
Pig
	
Ox
	
Man	8	0.887				
		0.461	0.823	0.777	0.208

TABLE 10.—COLLOID-EARLY-MODERATE GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep
	
Dog	2	0.692	0.626	0.167	0.140
		0.560	0.114
Pig
	
Ox
	
Man	2	0.600	0.523
		0.446

TABLE 11.—COLLOID-MODERATE GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep
	
Dog	3	0.554	0.446	0.423	0.099	0.098	0.085
		0.269	0.059
Pig
	
Ox
	
Man	7	0.492	0.366	0.355	0.116	0.090
		0.184	0.064

TABLE 12.—COLLOID-MODERATE-MARKED GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep
	
Dog	1	0.128	0.030
	
Pig
	
Ox
	
Man
	

TABLE 13.—COLLOID-MARKED GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep
Dog	1	0.115	0.022
Pig
Ox
Man

TABLE 14.—NORMAL-COLLOID GLANDS.

Animal.	No. Cases.	—Iodin Per Gm., Dried.—			—Iodin Per Gm., Fresh.—		
		E.	M.	A.	E.	M.	A.
Sheep
Dog
Pig
Ox
Man	8	3.230 1.100	1.653	1.942

HYPERPLASTIC GLANDS

The two series of hyperplastic glands, "normal" and "colloid," while separate and distinct anatomically, are alike chemically (iodin). That is, the iodine varies inversely with the degree of active hyperplasia, whether the hyperplasia occurs on the basis of a normal or of a colloid gland. This is illustrated very clearly in the curves (Figs. 8 and 9) of the two series. Here it is seen that the general trend of the curve is the same for all the animals examined, and also for both the normal and the colloid series. There are twenty-three cases of active hyperplasia in the normal series and seventeen cases in the colloid series.

1. First taking up the hyperplasias of the normal series:* The most striking and perhaps the most important fact brought out is the great

* See Tables 1, 7 and 15.

drop in the iodine content that occurs before histological changes are noticed. This is equally true of all the animals (see normal series' curve, Fig. 8). Reference to Table 15 shows that the lowest normal iodine content (1.307 mgm.) is well above the highest iodine content (1.077 mgm.) of the hyperplasias. This is also true of all the animals. It indicates that there is a quite constant lower limit in the iodine content necessary for the maintenance of normal gland structure and if the iodine falls below this limit, hypertrophic or hyperplastic changes begin. In our normal thyroid series the lowest iodine content per gram of dried gland associated with normal structure, and the highest iodine content associated with hyperplastic changes run as follows: For man, 1.307 and 1.077; for the dog, 1.990 and 1.296; for the sheep, 1.247 and 0.677; for the ox, 2.730 and 2.676, and for the pig, 1.538 and 1.158 mgm.

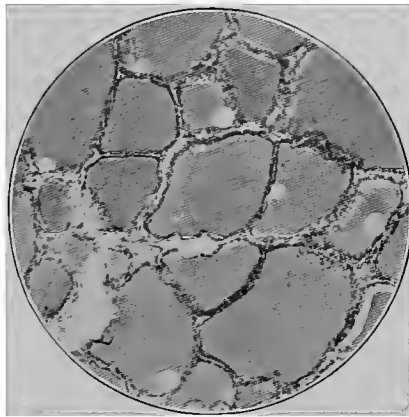


Fig. 1.—Normal thyroid (human). From a male, white subject, aged 40, dead of aortic stenosis. Iodine per gram of dried thyroid in milligrams—2.861. The sections represented in these illustrations were taken from the routine files of our human material. This material was hardened in 4 per cent. formalin. The sections were cut in celloidin and stained with hematoxylin and eosin. The magnification is the same in all, viz., Leitz, ocular IV, objective III = 95 diameters. Figures 1 to 4 represent the "Normal" or "Primary" series of hyperplasias.

Just as the earliest histological variations from the normal are the most important in the anatomical study of goiter formation, so also are the earliest deviations from the lowest iodine content compatible with normal structure. As we have just seen, the iodine content of normal glands varies within extremely wide limits, so also does the iodine content of pure colloid glands. But, on the other hand, the lowest iodine content compatible with normal structure and the highest iodine content associated with the hyperplastic changes vary within extremely narrow limits.

and, further, these limits are practically the same for four out of the five animals studied. (Why the ox thyroids should show an exceptionally high lower limit of iodine compatible with normal gland structure is not clear. In an earlier paper we have suggested it might be a biological [species] characteristic, inasmuch as these animals have relatively small thyroids.) It will be recalled that in the normal glands the highest amounts of iodine observed were also quite constant, being 4.614, 4.722, 4.153, 4.768, and 3.691 mgm. per gram of dried gland, for sheep, dog, pig, ox and man respectively. This observation, when taken in connection with the quite constant lower limit of iodine necessary for the maintenance of normal structure, adds weight to the view first suggested by the iodine feeding experiments—viz., that there is a definite limit to the combining capacity of the protein for iodine, and that any excess of iodine beyond this is excreted. Such a view would accord with the fact

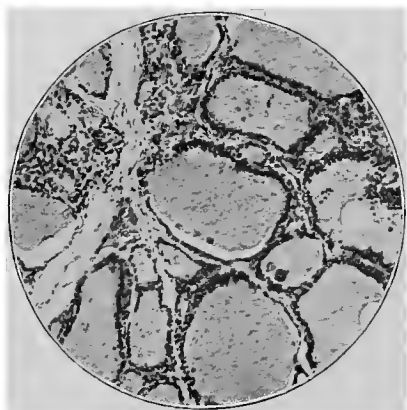


Fig. 2.—Early glandular hyperplasia. From a male, white, healthy subject, aged 30, dead of fracture of the skull, from an accidental fall. Iodine per gram of dried thyroid in milligrams = 0.877.

that iodine given to animals with glands in the stage of active hyperplasia has an action like desiccated thyroid, in that it increases the nitrogenous excretion and causes loss of body weight, while iodine *not* in the form of desiccated thyroid administered to dogs with histologically normal or colloid glands does not produce these effects on metabolism.

Passing to the other degree of hyperplasia it is seen that, instead of the great drop in the iodine content noted between “normal” and “normal-early” glands, the loss of iodine, while progressive, is more gradual and reaches its lowest point in the marked glandular hyperplasia group. This is true for all animals. Of the seven cases of marked glandular hyperplasia six were from cases of exophthalmic goiter and one from a case

of pernicious anemia. This is important. In the first place, it shows that in this locality the goiters of the exophthalmic group constitute the most frequent types of pure marked glandular hyperplasia, although we have frequently seen nearly as marked types of hyperplasia without the clinical complex of exophthalmic goiter. It also indicates that these forms are less frequently treated with iodine-containing compounds than are the forms occurring in childhood, puberty, pregnancy, etc.

2. The colloid series of hyperplasias (see Fig. 9 and Tables 8, 13 and 16) is in general similar to that of the normal series. We have observed the complete series in the dog. Our human series is incomplete, for the reason that complicating factors such as hemorrhages and scar formations, the result of previous hyperplasia, were present, and, having excluded such cases from the normal series, we had also to exclude them from this (colloid) series. The reason for exclusion

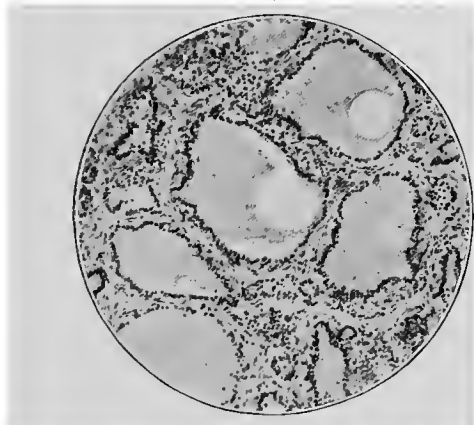


Fig. 3.—Moderate glandular hyperplasia. From a male, white subject, aged 31, dead of typhoid fever with intestinal perforation. Iodin per gram of dried thyroid in milligrams = 0.615.

was, in both series, the possibility of these complications modifying the findings. The general histological picture and the iodine contents of the colloid series are similar to those of the normal series. In the dog the normal and colloid series are parallel. In the human colloid series, as in the normal series, the most striking feature is the great drop in the iodine content that occurs in pure colloid glands before hyperplastic changes begin. Its physiological significance is the same and means that colloid glands are the nearest to normal that glands which have once undergone hyperplasia can become; also, that colloid glands react to the same stimuli as do normal glands. That the colloid series should show more irregularities than the normal series is to be expected.

First, the size of colloid glands is more variable, as compared with the quite constant size of the normal glands; therefore, the same total amount of iodine in glands of variable size would give quite variable iodine content per gram of dried gland. Most of the large glands, however, were complicated by hemorrhage or degenerative changes and were not used. Second, the duration of the goiter, the presence of cysts, hemorrhage or degenerations, interference with the normal lymphatic drainage by pressure, fibrosis, etc., the effects of medications (*x-ray*, etc.), all modify the iodine-containing capacity of the tissue and its physiological value to the organism. In consequence of the presence of these many factors it is noteworthy that the parallelism between colloid and normal glands in the human series should be so close. In the lower animals, where many of these modifying factors are absent, a still closer parallelism exists.

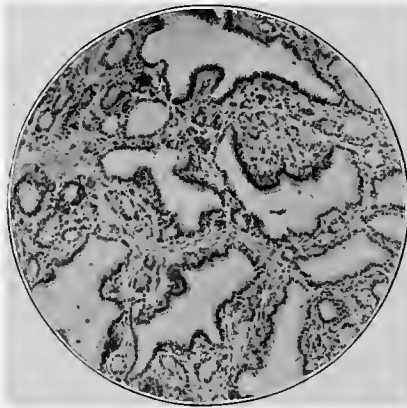


Fig. 4.—Marked glandular hyperplasia. From a case of exophthalmic goiter in a female subject, aged 22, dead following operation. Iodine per gram of dried thyroid in milligrams = 0.292.

COLLOID GLANDS *

There were twenty-five human glands in the colloid group. The extremes of iodine content were 3.914 and 0.784 mgm. per gram of dried gland. These extremes are somewhat greater than those of normal glands. So also colloid glands of dogs show greater extremes (3.608 and 0.846 mgm.) than the normal glands of dogs. This is to be expected, for the reason that colloid glands are of more variable size (usually larger) than are normal glands, and also for reasons indicative of a more complicated life-history, many of the factors of which are still unknown

* See tables 8 and 16.

—e. g., the condition causing the hyperplasia, or the condition causing the involution (reversion). The mean and average iodine contents of colloid glands are but little below the mean and average of normal glands. This is probably accidental, for the reason that most of these cases are autopsy specimens, and many of them had received iodine medication. Reference to Table 16 shows that the iodine content of the colloid glands can be raised to the same degree as that of normal glands. It is also seen that the iodine contents of colloid glands are the nearest approach to those of normal glands that one meets, a fact which supplements their anatomical similarity to normal glands. Thus, just as in the normal series, so in the colloid series, the greatest drop in iodine content occurs between pure colloids and the first detectable hypertrophic or hyperplastic changes. With a single exception, clearly dependent on the

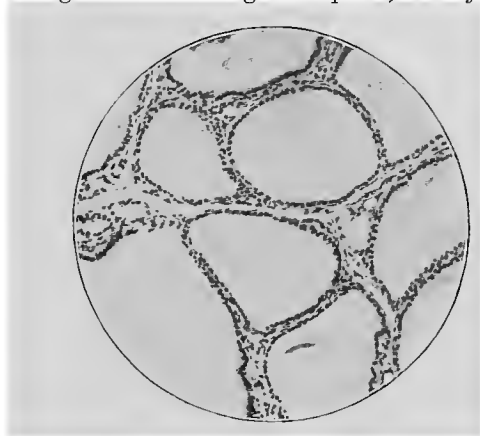


Fig. 5.—Colloid-early glandular hyperplasia. From a female, aged 21, dead of eclampsia with Cesarean section. Iodine per gram of dried thyroid in milligrams = 0.815. Figures 5 to 7 represent the "Colloid" or "Secondary" series of hyperplasias. (When this paper was sent to the publishers we had not obtained an uncomplicated specimen of colloid marked glandular hyperplasia.)

size of the gland, the lowest iodine content associated with a pure colloid gland is above the highest iodine content associated with active hyperplasia. In the case of colloid glands one can not say at what level of iodine per gram of gland hyperplastic changes would become manifest unless it is possible to work with glands more or less constant in size and free from complications. In our series as in our dog series it has been possible to work with colloid glands but slightly different from normal glands. With such a series it is easy to prove that colloid glands are similar to normal glands as regards their iodine contents.

NORMAL-COLLOID GLANDS *

This group of eight glands has been separated for the reason that histologically we could not decide whether they were normal or colloid. If they had undergone hyperplasia it was exceedingly slight. On the other hand, the size of the glands, their stroma and the outline of the vesicles did not fit the usual picture of normal glands. The iodine content closely resembles both normal and colloid glands as regards the extremes, mean and average. Ordinarily these glands would be considered normal, and they are normal as regards any physiological or clinical significance.

RELATION OF SEX, AGE, AND SIZE OF THE GLAND TO THE IODINE CONTENT;
IODINE IN THYROID TUMORS

We have not observed any difference in the iodine contents of thyroids referable to sex, either in man or in the lower animals. Slight differ-

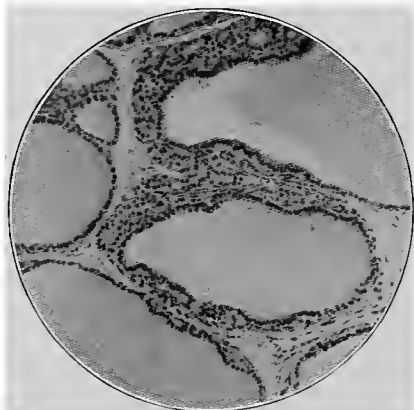


Fig. 6.—Colloid-moderate glandular hyperplasia. From a male, white subject, aged 22; clinical diagnosis; exophthalmic goiter. Patient operated on; recovered. Iodine per gram of dried thyroid in milligrams = 0.366.

ences in the iodine content, if present, could not be detected by the present methods of examination, while slight differences in the weights of the glands are more easily detected.

As regards *age*, Baumann⁴⁷ was the first to report differences. Since then all subsequent observers have confirmed his general conclusions, that iodine is lowest (in some cases absent) in infants' thyroids, gradually rises during the period of growth, continues more or less constant during the middle period of life (25 to 55 years), and finally falls slightly

* See Table 14.

47. Baumann: München. med. Wchnschr., 1896, xliii, 309.

in old age. As regards the presence of iodine in infants' thyroids, different observers have reported different results. Thus Weiss⁴⁸ reports 8 cases, the patients being from 24 days to 7½ years of age, all of which showed traces of iodine. Baumann⁴⁷ in 17 Freiburg cases, patients from 1 day to 7 years of age, found iodine present in 12. In 5 cases from Hamburg, from 5 days to 1 year of age, it was present in all. Von Rotsitzky⁴⁹ found iodine present in 6 of 8 cases, while Miwa and Stöltzner⁵⁰ found iodine in all of the 6 cases examined. Oswald⁵¹ also reports positive findings in all his cases. Jolin⁵² found iodine present in 20 of 27 cases examined. We have examined 10 subjects under one year of age and found iodine present in all. The highest was 0.482 mgm. per gram of dried gland, the lowest (an infant 1 month old) 0.027 mgm. per gram of dried gland. We have not examined any human thyroids at birth. In puppies whose mothers have been fed iodine we have detected

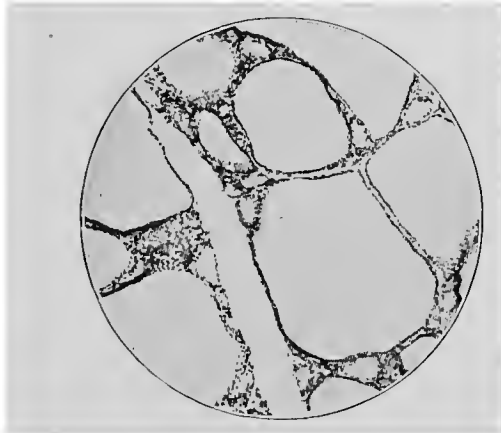


Fig. 7.—Colloid goiter. From a female subject, aged 19; case clinically diagnosed as severe exophthalmic goiter; patient had been treated for past six months by the internal administration of iodine; operated on, recovered. Iodine per gram of dried thyroid in milligrams = 4.614.

it in glands at birth in all cases; while we have not detected any iodine in the thyroids of puppies whose mothers had not been fed iodine during pregnancy. Nagel and Roos⁵³ have recorded similar observations. Hunt and Seidell⁵⁴ from the results of their examinations and experiments

48. Weiss: München. med. Wchnschr., 1897, xlv, 6.

49. Von Rotsitzky: Wien. klin. Wchnschr., 1897, x, 823.

50. Miwa and Stöltzner: Jahrb. f. Kinderh., 1897, xlv, 871.

51. Oswald: Ztschr. f. physiol. Chem., 1897, xxiii, 265.

52. Jolin: Festschr. f. O. Hammersten, 1906.

53. Nagel and Roos: Arch. f. Anat. u. Physiol. Supplementary Volume, 1902, p. 267.

54. Hunt and Seidell: Bull. 47, P. H. and M.-H. S., 1909, p. 49.

favor the view that iodine is not uncommonly absent at birth and that the protection which such thyroids offer to mice against acetonitrile poisoning may be due to some other constituent of the protein. From the above references of recorded observations it is seen that iodine to the extent of mere traces has been found in most cases. However, findings negative to the tests at present in use, do not mean that iodine was altogether absent, and before it can be said that iodine is normally absent at birth more accurate methods of iodine determination must be devised. There is no doubt that iodine may be absent (undetectable) at birth, for the same reasons that it is in older animals (hyperplasia, cretinism).

In old age there is a slight decrease of iodine, associated with and perhaps parallel with senile atrophy. Thus, in our series, there were seven (not included in the tables) normal senile glands. The highest iodine content was 1.584 mgm., the lowest 1 mgm., and the average 1.299 mgm. per gram of dried gland, as compared with 3.691, 1.307, and 2.171 mgm. respectively for uncomplicated histologically normal glands. In conclusion it may be stated that, while age bears a quite constant relation to the iodine content, it is one of the least important factors influencing the iodine content.

The relation of the total iodine to the size of the thyroid, when taken by itself, has little value. This relationship has been the subject of many controversies between those who sought to show that iodine was related to goiter formation and those who sought to show that iodine was merely accidental. All workers have agreed that in general goiters tend to contain less iodine than normal glands. To this there are many exceptions, however. These exceptions could probably be explained, as we have previously pointed out, by comparing the histological structures with the iodine contents. We have made such comparisons in the sheep, dog and man, and have found that, as a rule, colloid goiters have more iodine (total) than have normal glands, while active hyperplasias for all the animals examined have much smaller total iodine contents than normal glands.⁵⁵ Therefore, any discussion of the relation of iodine to the size of the glands is useless unless it is based on the more important factor of histologic structure. In general it may be stated that all actively hyperplastic glands have a smaller total iodine content than normal glands; and that the total iodine varies inversely with the degree of glandular hyperplasia. On the other hand, all pure colloid glands usually have more iodine than the minimal normal content (though, as a rule, per gram of dried gland, colloid glands have less iodine than normal

55. Marine and Lenhart: Further observations on the relation of iodine to the structure of the thyroid gland in the sheep, dog, hog and ox. *THE ARCHIVES INT. MED.*, 1909, iii, 66.

glands). The total amount of iodin that a gland may contain obviously depends on its size, the accidental circumstances of food, medication, locality, etc. Oswald,⁵⁶ and all subsequent observers, have shown that the colloid of colloid glands (goiters) may contain as high a percentage of iodin as the colloid of normal glands, and that such colloid has the same physiological activity as colloid from normal glands.

The presence of iodin in thyroid tumors is also of interest and may be referred to at this time. It is the rule to find iodin in fetal adenoma. We have examined nine such tumors and have found iodin in eight. The highest iodin content was 0.593 mgm. per gram of dried tumor, while the average content of the eight cases was 0.174 mgm. The specimen in which no iodin was demonstrable was removed at operation, together with some of the surrounding original thyroid tissue, which histologically was pure colloid gland (goiter) and contained 1.922 mgm. of iodin per gram of dried gland. The tumor had the usual characteristics of fetal adenoma. It was a round, encapsulated, soft, grayish, cellular mass of tissue 4 by 4 c.m., and histologically was composed of uniform, small, undistended alveoli lined with cubical epithelium. In these benign tumors the iodin content varies with the structure just as in the simple hyperplasias, being lowest in the very cellular actively growing tumors and highest in those that have undergone involution (reversion) to the colloid state. We have examined metastases from two cases of thyroid carcinoma in dogs, but found no iodin.

SUMMARY AND DISCUSSION

When all the glands are arranged according to their histological structures with normal or colloid glands at one end and the marked hyperplasias at the other, as in the full tables (Nos. 15 and 16), it is seen that the normal and colloid glands have the highest and the marked hyperplasias the lowest iodin contents. This is true for all the animals examined. It also shows that the iodin varies with the amount of stainable colloid; inversely with the size of the glands (in hyperplasias) and inversely with the degree of active hyperplasia. These relations were earlier shown to be true of dog, sheep, ox and pig thyroids. Such constant relations of iodin to the gland structure can not be accidental when taken in connection with other established facts. Thus Roos⁴⁸ has shown that the physiological action of desiccated thyroid (as ascertained by the nitrogen excretion) varies directly with the amount of iodin in organic combination. Oswald⁵¹ repeated this work, using thyroglobulin from normal and from goitrous glands with the same results. He also showed that the action of thyroglobulin of goitrous glands was

56. Oswald: Virchow's Arch. f. path. Anat., clxix, 444.

not different (qualitatively) from that of normal thyreoglobulin. Hunt and Seidell⁵⁴ have obtained similar results with the acetonitrile indicator. Although at first disputed, it is now abundantly confirmed that the beneficial effect, clinically, of desiccated thyroid on goiter is parallel with its iodine content. We have shown⁵⁵ that the administration of iodine to animals with active hyperplasia has the same pharmacological effect that desiccated thyroid has on normal animals. Further, it has been shown that feeding any iodine-containing compound very quickly (in three or four weeks) causes hyperplastic glands to revert, and that this change is associated with the rapid accumulation of iodine in the gland. It is of little or no consequence whether the hyperplasia occurs in man or animals, or whether it is associated clinically with myxedema (cretinism) or with exophthalmic goiter. So also it has been pointed out that iodine prevents the occurrence of fetal thyroid hyperplasia in puppies whose mothers have had most of their thyroids removed. Also it has been shown that iodine will prevent the compensatory hyperplasia following partial removal of the thyroid. In the presence of sufficient doses of iodine all true hyperplasia is prevented. Such evidence, it seems to us, is the highest or biological proof that iodine is an active, perhaps the most active, constituent of the thyroid secretion. Recent observations by Fassin⁵⁷ and Marbé⁵⁸ indicate that iodine markedly raises the alexic (opsonic) activity of the blood serum. This is perhaps of great interest in that it may tend to explain why iodine benefits certain chronic inflammatory processes, and also why cretinoid animals manifest very low resistance to infectious agents. All of these facts show that during the active growth of the goiter there is a deficiency of iodine in the thyroid. This general observation recalls to mind the extensive chemical analyses that were made by Prevost and Maffoni,⁵⁹ by Niepce,⁶⁰ by Marchand⁶¹ (quoted by St. Lager), and, more particularly, by Chatin,⁶¹ and their conclusion that goiter was due to lack of iodine. They attributed the deficiency to a lack of iodine in the water and air, pointing out that along the seacoast, and in localities where iodine was present in relatively large quantities, goiter did not frequently occur. Their methods of chemical analysis were faulty, and their conclusion was easily overthrown by the extensive examinations of water, air and soil that followed. It seems now firmly established that there is an actual deficiency of iodine in the thyroid during the stage of active hyperplasia. On the other hand, the vast collections of statistical evidence on the iodine con-

57. Fassin: *Compt. rend. Soc. de biol., Paris*, 1907, lxii, 390; 1909, lxvi, 457.

58. Marbé: *Compt. rend. Soc de biol., Paris*, 1909, lxvi, 432.

59. Maffoni: *Atti d. Accad. med.-chir. de Torina*, 1846, ii, 453.

60. Niepce: *Traite du goitre et du crétinisme*, 1852, ii.

61. Quoted by St. Lager: *Etudes sur les causes du crétinisme*, Paris, 1867.

tent of waters and foods, as well as the occurrence of goiter in some and not in other members of groups of men living under the same conditions of food and water, as in schools, barracks, garrisons, etc., would leave little doubt that the deficiency of iodine was not commonly due to a lack of iodine intake. Therefore, it would seem that some other agents or factors were operating in these cases. As is well known, many, indeed almost all the ordinary mineral substances, infectious agents, etc., have from time to time been accused. The infectious origin has been supported by Virchow, Bircher, Kocher, Hirsch and others, and reached its greatest popularity during the early period of bacteriological investigation (1850-85). Since Schiff, Wagner and Halsted²⁶ first established the fact that compensatory hyperplasia normally followed removal of the gland, and that this hyperplasia was in no way different from the changes in developing goiters, the infectious theory has been declining, while the nutritional or metabolic view has been gaining. To be sure, changing the water-supply and boiling the water have been associated with a decrease of goiter. But this could scarcely be any greater argument for an infectious origin of goiter than for a metabolic (chemical) one. But, whatever the ultimate causal factor is shown to be, it is certain that there is a deficiency of iodine in the gland, and that this deficiency of iodine in the gland is not usually due to a lack of iodine intake, but is dependent on a lack of absorption or assimilation of iodine. And it is our belief that one or more chemical substances will be found which are antagonistic to or inhibit the normal absorption or assimilation of iodine.

RELATION OF IODINE CONTENT AND HISTOLOGICAL STRUCTURE TO DISEASE PROCESSES IN GENERAL

Any discussion of the relation of the thyroid to disease processes must take account of both the histological structure and the iodine content of the thyroid, since these two factors have the following constant relation: The iodine content varies inversely with the degree of active hyperplasia. Is this relation merely accidental or is it one of cause and effect? Sufficient data are now available to prove that this relation is not accidental. These data may be summarized as follows:

1. Partial removal of the thyroid is normally followed by compensatory hyperplasia of the remaining portion. The extent of the resulting hyperplasia is known to depend on the age of the animal, the amount of gland removed and the quality of the food. Horsley,⁶² Halsted,²⁸ Marine,⁴ Marine and Williams.⁴

62. Horsley: Proc. Roy. Soc., London, 1886, xl, 6.

2. Withholding iodine increases the extent of the hyperplasia following partial removal (Marine⁴), and also causes hyperplasia without partial removal (Baumann^{42, 47}).

3. The administration of iodine causes active hyperplasias of all animals to revert to the colloid state; prevents the occurrence of active hyperplasia following partial removal of glands which otherwise would undergo hyperplasia.

4. The administration of iodine prevents hyperplasia of the thyroids of puppies from bitches in which three-fourths of the gland has been removed.

5. Normal thyroids of all the animals examined have the highest and marked hyperplasias the lowest iodine contents.

6. The administration of iodine-containing compounds to the animal in any form and by any method is rapidly followed by its storage in the thyroid in quantities that bear no relation to the iodine content of the other tissues.

7. The rapidity of accumulation and the amount of iodine thus taken up by the thyroid depend on its size and the degree of active hyperplasia.

8. The physiological activity, as determined by the nitrogen excretion (Roos,⁴⁸), by the loss of body weight (Marine and Lenhart^{2, 55}), and by the acetonitrile reaction (Hunt,⁴⁴ Hunt and Seidell⁵⁴), depends principally on the amount of iodine in organic combination.

9. It has been shown (Marine and Williams,⁴ Marine and Lenhart^{2, 55}) that in dog, sheep, pig, ox and human thyroids there is a quite constant minimum percentage of iodine necessary for the maintenance of normal gland structure.

While practically nothing is known of the causes leading to the iodine deficiency in the animal, the above facts, beyond doubt, show that the increased growth and divisional activity of the thyroid cells are intimately associated with a decrease of iodine, and that the increased iodine content is similarly associated with a decreased growth and divisional activity of the thyroid cells. On this basis one would expect to find thyroid changes resulting from any cause which diminished the intake or assimilation of, or increased the body demands for iodine, and that, therefore, all thyroid changes would be compensatory in nature and secondary to more fundamental causes, perhaps nutritional in nature. Also we would expect to find active hyperplasia (goiter) always preceded and accompanied by other systemic disturbances, especially those of a nutritional nature. There are other views regarding the nature of thyroid hyperplasia. Thus it is looked on by many as an infectious process in which some specific organism plays a primary rôle. The argu-

ments for this view are of the same nature as those advanced in support of the microbic etiology of cancer. They need not be discussed here.

Another view, advanced by Gauthier⁶³ and Moebius,⁶⁴ is that certain types, at least, of thyroid hyperplasia are primary processes. This view is particularly applied to exophthalmic goiter, and implies that the thyroid changes are idiopathic and spontaneous, and that the thyroid abnormality by means of a hypersecretion or perverted secretion causes the disease. Without going further into the almost countless theories regarding the nature of the thyroid reaction, most of which have only an historical interest, it may be said that the three views above mentioned are the only active ones at present and may be summarized as follows: 1. Active hyperplasia is a compensatory and secondary reaction to a disturbance of nutrition. 2. It is the result of a specific infectious agent. 3. It is a primary thyroid disturbance.

A great variety of diseases are associated with or accompanied by noticeable thyroid changes. Thus rickets, lymphatism, chlorosis, cretinoid states and osteomalacia (?) are practically always associated with anatomical changes in the thyroid. Many of the prolonged infectious diseases, as lues, typhoid fever, influenza, acute articular rheumatism and tuberculosis, are frequently associated with or followed by thyroid hyperplasia. In individuals with adenoids and enlarged tonsils (lymphatism) (?), in abnormally fat children and in adiposis dolorosa,⁶⁵ the association is not infrequent. In conditions in which mental and nervous fatigue have lasted for prolonged periods of time, as in neurasthenia, and in prolonged mental states produced by worry, shock, anxiety, overwork, etc., thyroid changes are frequently observed. Also there is a particular association of thyroid changes with the systemic changes taking place at puberty; with the menstrual function; with pregnancy and lactation, and with the menopause. Lastly, thyroid changes are perhaps most frequently seen in the poorly fed and poorly nourished young (puppies, lambs, calves and children).

While all the groups of disease processes above enumerated have long been associated with thyroid changes, by some writers as cause and effect, by others as accidental, it is clear that they represent only a portion of the factors or agents capable of instituting conditions of nutrition favorable for the development of thyroid hyperplasia. Thus, while thyroid hyperplasia (goiter) may occur anywhere, it is particularly associated with certain localities. Thus far nothing specific in the geology, climate, food or otherwise has been found to account for this increased

63. Gauthier: *Rev. de méd.*, 1890, x, 409.

64. Moebius: *Centralbl. f. Nerven.*, 1887, x, 225.

65. Price: *Am. Jour. Med. Sc.*, 1909, cxxxvii, 705. Guillian and Alquier: *Arch. de méd. expér. et d'anat. path.*, 1906, xviii, 680.

TABLE 15.—NORMAL SERIES—MAN

Series No.	Age.	Sex.	Autopsy or Surgical.	Anatomical or Clinical Diagnosis.	Size of Gland.	Visible Colloid.	Normal.	Colloid.	Early.	Moderate.	Marked.	Per cent. Water.	Iodin, per gm., Dried.*	Iodin, per gm., Fresh.*	Remarks.
H 232....	45	M.	S.	Exophthalmic goiter.....	?	Absent.....	+	0.118	Slight signs of myxedema.
H 364....	31	F.	S.	Exophthalmic goiter.....	?	Absent.....	+	0.125	Definite signs of myxedema.
H 251....	25	M.	S.	Exophthalmic goiter.....	?	Absent.....	+	0.277	0.060	
H 267....	20	M.	S.	Exophthalmic goiter.....	?	Absent.....	+	0.292	Very severe type; marked lymphoid hyperplasia; autopsy.
H 237....	41	F.	A.	Pernicious anemia.....	Slightly enlarged.	Absent.....	+	0.323	
H 214....	37	F.	S.	Exophthalmic goiter.....	?	Visible.....	+	0.544	0.109	Definite signs of myxedema.
H 222....	50	F.	S.	Exophthalmic goiter.....	?	Absent.....	+	0.584	0.115	
H 226....	35	M.	A.	Cerebrospinal meningitis.....	?	Absent.....	+	0.332	Negro: status lymphaticus.
H 343....	10	M.	A.	Acute rheumatic endocarditis.....	Slightly enlarged.	Visible.....	+	0.480	
H 225....	42	M.	A.	Nephritis—cerebral hemorrhage.....	Slightly enlarged.	Visible.....	+	0.615	
H 270....	35	M.	S.	Exophthalmic goiter.....	?	Visible.....	+	0.807	
H 258....	5	M.	A.	Hemorrhagic purpura and lymphatic leukemia.	Slightly enlarged.	Visible.....	+	0.406	
H 368....	24	M.	A.	Gunshot wound of lungs.....	Normal.	Visible.....	+	0.554	
H 224....	59	M.	A.	Tuberculous pneumonia.....	Below normal.	None.....	+	0.738	
H 315....	52	M.	A.	Nephritis—cerebral hemorrhage.....	Normal.	Visible.....	+	0.738	
H 233....	22	F.	A.	Puerperal endometritis.....	Moderately enlarged.	Visible.....	+	0.861	
H 334....	30	M.	A.	Fractured skull.....	Normal.	Visible.....	+	0.877	Normal healthy adult.
H 267....	50	M.	A.	Sudden death; cause not ascertained.	Slightly enlarged.	Visible.....	+	0.923	Dead after herniotomy.
H 328....	30	M.	A.	Typhoid fever.....	Slightly enlarged.	Visible.....	+	1.077	
H 303....	42	F.	A.	General peritonitis.....	Slightly enlarged.	Visible.....	+	0.615	
H 259....	21	M.	S.	Exophthalmic goiter.....	Normal.	Normal.....	+	0.769	0.196	

H-307.	40 M.	A.	Nephritis.	Slightly enlarged.	Visible.	+	+	0.846	0.216	Negro.
H-244.	35 M.	A.	Morphin poisoning.	Slightly enlarged.	Visible.	+	+	0.984		
H-297.	27 M.	A.	Hemorrhagic encephalitis(?)	Normal.	Abundant.	+	+	1.307		Negro.
H-308.	40 M.	A.	Lobar pneumonia	Normal.	Normal.	+	+	1.461	0.310	Gland weighs 26 gms; absolutely normal in gross appearance.
H-310.	40 F.	A.	Generalized tuberculosis.	Normal.	Normal.	+	+	1.538		
H-273.	18 F.	A.	?	Normal.	Normal.	+	+	1.553		
H-298.	28 M.	A.	Gunshot wound of lungs.	Normal.	Normal.	+	+	1.661	0.403	Generalized skin lesions; anatomical diagnosis not made.
H-298.	42 F.	A.	Myocarditis	Normal.	Normal.	+	+	1.692	0.443	Healthy young adult.
H-345.	30 M.	A.	Gunshot wound of abdomen.	Normal.	Normal.	+	+	1.692	0.403	Cesarean section.
H-353	61 M.	A.	Carcinoma of stomach	Normal.	Normal.	+	+	1.692		Healthy young adult.
H-290.	40 M.	A.	Suppurative cholecystitis.	Normal.	Normal.	+	+	1.692		
H-216.	38 M.	A.	Liver abscess	Normal.	Normal.	+	+	1.769	0.451	
H-287.	45 M.	A.	Aortic aneurism	Normal.	Normal.	+	+	1.876		
H-302.	45 F.	A.	Carcinoma—ovary(?)	Normal.	Normal.	+	+	2.000		
H-347.	43 M.	A.	General peritonitis.	Normal.	Normal.	+	+	2.153		
H-312.	40 M.	A.	Fracture of skull.	Normal.	Abundant.	+	+	2.230		
H-352.	21 M.	A.	Miliary tuberculosis.	Normal.	Visible.	+	+	2.307		
H-323.	45 M.	A.	Pernicious anemia.	Small.	Normal.	+	+	2.461		
H-283.	30 M.	A.	Endocarditis, acute.	Normal.	Normal.	+	+	2.537		
H-221.	25 M.	A.	Generalized tuberculosis.	Normal.	Normal.	+	+	2.614		
H-366.	58 M.	A.	Carcinoma of esophagus.	Normal.	Normal.	+	+	2.615		
H-286.	? M.	A.	Apoplexy.	Normal.	Visible.	+	+	2.691		
H-278.	40 M.	A.	Aortic stenosis.	Normal.	Normal.	+	+	2.861		
H-243	50 M.	A.	Aneurism.	Normal.	Abundant.	+	+	3.384		
H-349.	50 M.	A.	Generalized tuberculosis.	Normal.	Normal.	+	+	3.691		

* Iodin figures are in mgm.

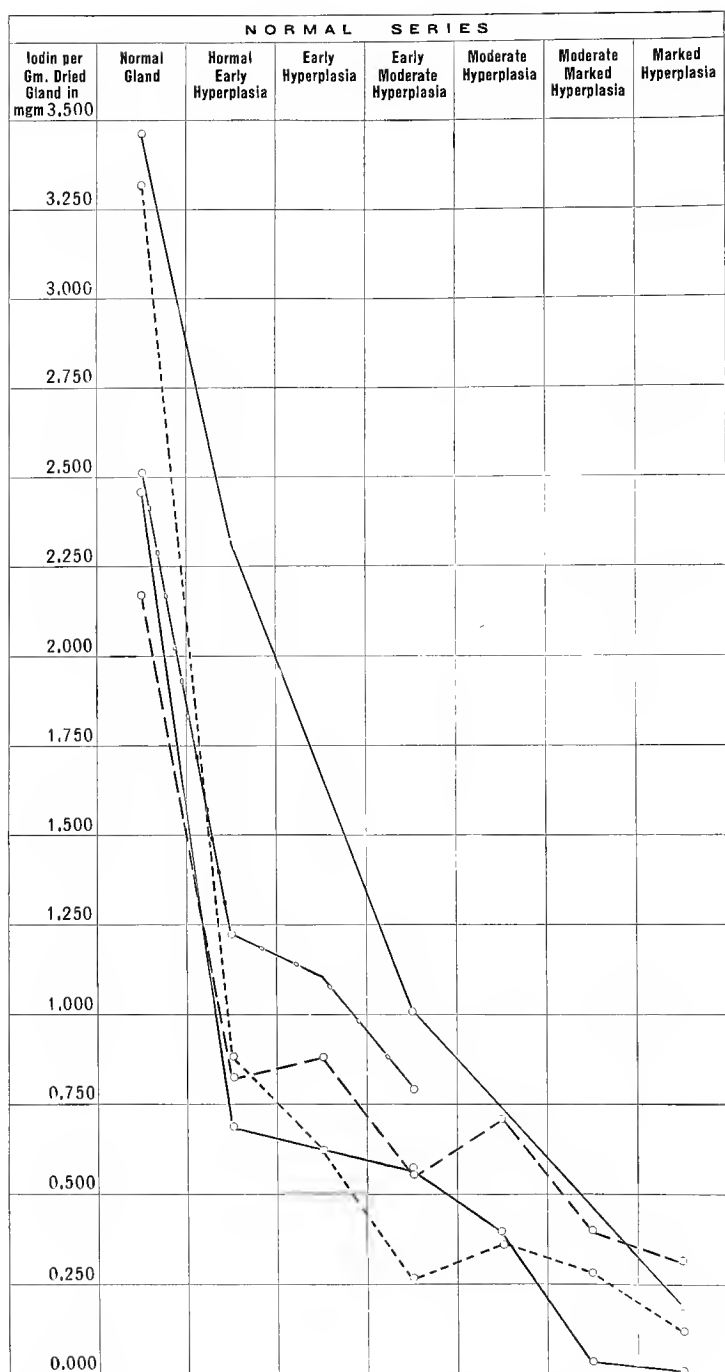


Fig. 8.—Curves compiled from the average iodine contents per gram of dried gland of the normal series of hyperplasias. The solid line represents the curve for the ox, the dotted line the curve for the dog, the line composed of short and long dashes the curve for the sheep, the line with short dashes the curve for man, and the line composed of long dashes and circles the curve for the pig.

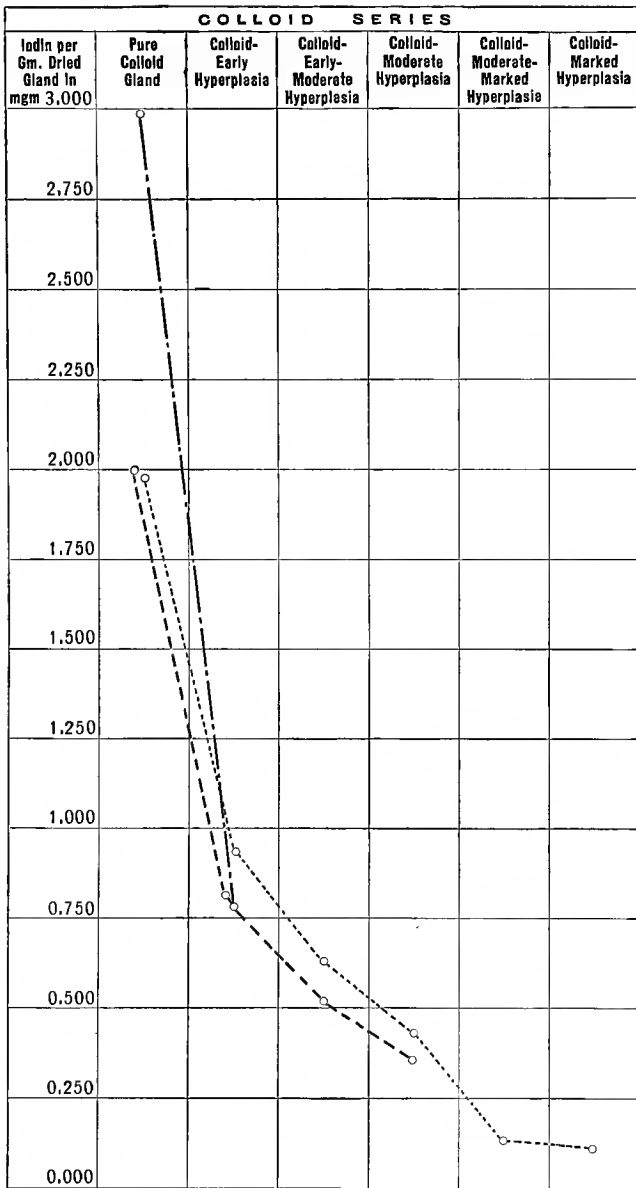


Fig. 9.—Curves compiled from the average iodine contents per gram of dried gland of the colloid series of hyperplasias in man, the dog and the pig, represented, respectively, by lines of the same character as in Figure 8.

TABLE 16.—COLLOID SERIES—MAN

Series	Sex.	Age.	Autopsy or Surgical.	Anatomical or Clinical Diagnosis.	Size of Gland.	Visible Colloid.	Colloid.	Colloid Early.	Colloid Mod.	Colloid Marked.	Per ct. Water.	Iodin, per gm., Dried.	Iodin, per mgm., Fresh.
H-263....	M.	28	A.	Rachitic dwarf; empyema.	Moderately enlarged.	Visible.....	+	+	+	+	...	mgm. 0.184	mg.
H-356. ...	M.	15	S.	Colloid goiter.....	Moderately enlarged.	Visible.....	+	+	+	+	...	0.261	0.064
H-264. ...	F.	...	S.	Moderately enlarged.	Visible.....	+	+	+	+	...	0.338	
H-369. ...	M.	24	S.	Exophthalmic goiter.	Moderately enlarged.	Visible.....	+	+	+	+	...	0.366	
H-274. ...	M.	68	A.	Cerebral hemorrhage.	Moderately enlarged.	Visible.....	+	+	+	+	...	0.384	
H-301. ...	M.	72	A.	Chronic interstitial nephritis.	Slightly enlarged.	Visible.....	+	+	+	+	...	8.461	
H-230. ...	F.	73	A.	Senility; pneumonia..	Slightly enlarged.	Visible.....	+	+	+	+	...	0.492	0.116
H-268. ...	F.	...	S.	Marked enlargement.	Visible.....	+	+	+	+	...	0.446	
H-365. ...	F.	15	S.	Colloid goiter	Marked enlargement.	Visible.....	+	+	+	+	...	0.600	
H-231. ...	M.	16	S.	Colloid goiter.....	Marked enlargement.	Visible.....	+	+	+	+	...	0.595	
H-235. ...	F.	29	A.	Carcinoma of ovary...	Moderate enlargement.	Normal.....	+	+	+	+	...	0.615	
H-247. ...	M.	45	A.	Hemorrhage into medulla oblongata.	Normal.....	Normal.....	+	+	+	+	...	0.769	
H-277. ...	F.	22	A.	Eclampsia	Moderate enlargement.	Visible.....	+	+	+	+	...	0.815	
H-148. ...	F.	30	A.	Septicemia.....	Slightly enlarged.	Visible.....	+	+	+	+	...	0.831	0.208
H-282. ...	M.	70	A.	Prostatic hypertrophy.	Slightly enlarged.	Visible.....	+	+	+	+	...	0.846	
H-341. ...	F.	64	A.	Carcinoma of jejunum.	Moderate enlargement.	Visible.....	+	+	+	+	...	0.861	
H-284. ...	F.	30	A.	Tuberculous peritonitis.	Moderate enlargement.	Visible.....	+	+	+	+	...	0.887	
H-285. ...	F.	40	A.	Pulmonary embolism.	Markedly enlarged.	Abundant.	+	+	+	+	...	0.784	
H-262. ...	F.	32	S.	Exophthalmic goiter.	Abundant.	+	+	+	+	...	0.828	
H-266. ...	F.	...	S.	Abundant.	+	+	+	+	...	0.984	
H-257. ...	F.	40	S.	Cyst of thyroid.....	Abundant.	+	+	+	+	...	1.215	
H-212. ...	F.	23	S.	Exophthalmic goiter.	Abundant.	+	+	+	+	...	1.276	0.304
H-309. ...	M.	70	A.	Cerebral hemorrhage.	Small.....	Visible.....	+	+	+	+	...	1.277	
H-317. ...	M.	35	A.	Generalized tuberculosis.	Slightly enlarged.	Normal.....	+	+	+	+	...	1.277	
H-252. ...	M.	16	A.	Acute endocarditis....	Marked enlargement.	Abundant.	+	+	+	+	...	1.507	
H-250. ...	M.	40	A.	Multiple fractures; sepsis.	Normal.....	Abundant.	+	+	+	+	...	1.507	0.345
H-228. ...	M.	35	A.	Fracture of skull.....	Small.....	Normal.....	+	+	+	+	...	1.538	
H-220. ...	M.	35	A.	Lobar pneumonia	Normal.....	Normal.....	+	+	+	+	...	1.540	0.381
H-326. ...	F.	30	A.	Cirrhosis of liver; luetic.	?	Abundant.	+	+	+	+	...	1.692	
H-330*. ...	F.	20	A.	Pyosalpyx; general peritonitis.	Slightly enlarged.	Normal.....	+	+	+	+	...	1.769	
H-348a. ...	F.	...	S.	Cystic colloid goiter..	Abundant.	+	+	+	+	...	1.922	
H-312. ...	M.	68	A.	Ulcer of stomach(?)..	Small.....	Normal.....	+	+	+	+	...	1.922	
H-233†. ...	M.	35	A.	Fracture of skull.	Slightly enlarged.	Abundant.	+	+	+	+	...	1.922	
H-229. ...	F.	49	A.	Carcinoma of bladder (urinary).	Slightly enlarged.	Abundant.	+	+	+	+	...	1.970	0.614
H-314. ...	M.	45	A.	Pernicious anemia...	Small.....	Normal.....	+	+	+	+	...	2.307	
H-362. ...	M.	56	A.	Chronic interstitial nephritis.	Normal.....	Abundant.	+	+	+	+	...	2.615	
H-275. ...	M.	50	A.	Carcinoma of urinary bladder.	Moderate enlargement.	Abundant.	+	+	+	+	...	2.861	0.701
H-294. ...	F.	33	A.	Ectopic gestation; peritonitis.	Moderate enlargement.	Abundant.	+	+	+	+	...	2.922	
H-225. ...	M.	27	A.	Cardiac disease; chronic nephritis.	Slightly enlarged.	Abundant.	+	+	+	+	...	3.153	
H-245. ...	M.	50	A.	Carcinoma of prostate.	Normal.....	Normal.....	+	+	+	+	...	3.507	0.798
H-290. ...	M.	54	A.	Chronic interstitial nephritis.	Slightly enlarged.	Abundant.	+	+	+	+	...	3.691	
H-227. ...	M.	40	A.	Lobar pneumonia	Slightly enlarged.	Abundant.	+	+	+	+	...	3.914	

* Negress. † Healthy young adult.

frequency. We believe, however, that some agency or factor will be found in these districts that operates to produce hyperplasia by interference with the normal chemical processes of the body.

As was first pointed out by Hale White,⁹ if one examines any large series of human thyroids he will find a considerable number showing hyperplastic changes in cases in which the subjects during life showed no symptoms known to be associated with thyroid disease. His observations have been abundantly confirmed, not only for man, but for the lower animals as well. Indeed, it is most striking in carnivora. Thus 90 per cent. of the dogs in this district have active thyroid hyperplasia, and yet, so far as we are at present able to detect clinically, most of these dogs are normal. This does not mean, however, that such animals have no symptoms directly associated or parallel with the thyroid changes. For we know that after these changes have reached a certain degree all animals show clinical manifestations. It rather indicates that the thyroid is extremely sensitive to stimuli and that the symptoms produced in most cases are below the present level of clinical detectability. In man the greater proportion of thyroids showing histological changes toward goiter formation are not associated with detectable clinical manifestations. Most of these milder degrees of thyroid changes spontaneously right themselves when the underlying or accompanying disease disappears, as, for example, the hyperplasia associated with influenza, or typhoid, or pregnancy, etc., rarely comes to clinical notice. Thus it is that all autopsy series show such a great proportion of thyroid changes without detectable clinical manifestations.

Thus far we have been discussing thyroid changes only, but it must not be overlooked that these changes are as a rule associated with other tissue reactions. The lymphoid tissues and bone marrow are very frequently hypertrophied as well. This association may be present in all the clinical forms of goiter, including cretinism. It is most frequently noticed, however, in exophthalmic goiter and in cretinism. This very common association with exophthalmic goiter was first recorded by Markham⁶⁶ and is now recognized as a constant accompanying condition in all the severe cases. There are differences of opinion as to the significance of these changes, particularly in exophthalmic goiter. Thus, Boit⁶⁷ and Capelle⁶⁸ regard the condition as lymphatism associated with exophthalmic goiter. Hansemann,¹⁶ Hirschlaff¹⁷ and others think that the

66. Markham: *Tr. Path. Soc., London*, 1858, ix, 163.

67. Boit: *Frankf. Ztschr. f. Path.*, 1907, i, 187.

68. Capelle: *Beitr. z. klin. Chir.*, 1908, lviii, 353.

thymic enlargement is due to thyroid toxins. Hart⁶⁹ thinks that the thymus toxins start the thyroid changes. Last, there is the view supported by Marie,⁷⁰ Hektoen,⁷¹ Marine⁴ and T. Kocher⁷² and others, that these changes are a part of the disease. Whether the association is merely coincident or is dependent on some other as yet unknown nutritional disturbance is not determined. The present knowledge would indicate a very close relationship between goiter and lymphoid hyperplasia and, since lymphoid hyperplasia is also common in rickets, chlorosis and lymphatism, it would indicate that if these diseases, in common with goiter, have specific causal agents, these agents are all frequently active at the same time and in the same individual.

Finally the question arises: Are the thyroid changes associated with the diseases above enumerated identical as regards their anatomy, their chemistry and their biological reactions? So far as we are able to detect these changes, they are identical. In all there is the lowering of the iodine inversely with the degree of hyperplasia. The histological picture is identical in all, and they react alike to iodine-containing compounds. The changes in exophthalmic goiter are considered by many to be separate and distinct, and will be discussed separately.

To sum up: It is seen that active hyperplasia accompanies and follows a great variety of clinical diseases: that it is far more commonly and easily detected anatomically than clinically; that with whatever disease associated, the anatomical changes are the same; the iodine content varies in the same way in all, and they all react alike to iodine-containing compounds; that changes in the lymphoid tissues are frequently observed along with goiter, and also with other diseases with which goiter is frequently associated. On this evidence we conclude that the thyroid changes are not specific or primary, but are only the result of stimuli, constant perhaps, arising in the course of many nutritional disturbances (diseases).

RELATION OF THE IODINE CONTENT AND THE HISTOLOGICAL STRUCTURE TO EXOPHTHALMIC GOITER⁷³

It is concerning the recognition and the separation of the essential from the accidental findings in exophthalmic goiter that the difficulties and controversies have arisen. This is true of both the clinical and the

69. Hart: München. med. Wchnschr., 1908, lv, 668.

70. Marie: Gaz. d. hôp., 1893, 202.

71. Hektoen: Internat. Med. Mag. Phila., 1896, iv, 584.

72. Arch. f. klin. Chir., 1908, lxxxvii, 131.

73. Dock (Jour. Am. Med. Assn., 1908, li, 1119) has lately reviewed the question of the appropriate name for this disease and we agree with him in preferring the term "exophthalmic goiter," though an objectionable one, to such designations as "Flajani's," "Parry's," "Graves'" or "Basedow's disease."

laboratory observations. The amazing quantity of literature that has accumulated about this disease in the past twenty-five years clearly indicates that neither clinical studies alone nor anatomical studies alone, nor the combination of these alone, will accurately define what should be included under the term exophthalmic goiter.

This disease is associated with and in all probability depends primarily on nutritional disturbances, the nature of which is not determined, and it is not even known whether they are fundamentally the same in all cases. The anatomical changes, the iodine relations and the general phenomena of the disease will be discussed in the order named. The views as to the relation of the anatomical changes may be grouped under three headings: (1) the view that the thyroid changes are constant and specific; (2) that the anatomical changes have no particular relationship to the disease; (3) that the anatomical changes (hyperplasia), while constantly present at some stage in all cases, are also present at some stage in all true goiters.

The view that the thyroid changes (hyperplasia) in exophthalmic goiter are constant and specific had been supported by Greenfield,¹³ Farmer,²⁵ Bramwell,¹² Hämig,⁷⁴ MacCallum,¹⁸ Lewis,²⁰ Ewing,¹⁹ Wilson²¹ and others.

The view that there is no particular relationship between the anatomical changes and the disease has been supported by Virchow,⁷⁵ Renaut and Brissaud,⁷⁶ Reinbach,⁷⁷ A. Kocher⁷⁸ and many others. These are the extremes. Neither view fully accords with the facts. On the one hand, the hyperplasia is not common to this disease alone, while, on the other hand, this hyperplasia occurs at some time in all true cases of exophthalmic goiter. The explanation of the fact that one often sees colloid goiter associated with the symptom-complex of exophthalmic goiter is that the thyroid may undergo very rapid histological changes without correspondingly rapid changes in the symptoms.

Thus we have seen cases with marked hyperplasia under the influence of small doses of iodine revert to colloid goiter in from three to four weeks, while the clinical manifestations remained practically the same. As a rule, however, the symptoms become less marked as the involution (reversion) to colloid goiter occurs. Thus the histological condition of the specimen at the time of removal may be quite different from what

74. Hämig: Arch. f. klin. Chir., 1897, lv, 1.

75. Virchow: Die krankhaften Geschwülste, iii, 75.

76. Renaut and Brissaud: Semaine méd., 1895, No. 39.

77. Reinbach: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1901, viii, 247.

78. Kocher, A.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1902, ix, 1.

it would have been even two weeks before. Similar histological changes to those in exophthalmic goiter are also seen in all developing functional hyperplasias of man and animals. There are differences of degree and differences depending on the age of the animal, the number of times the gland has reverted and undergone hyperplasia, the presence of complications, etc., as outlined above. The reaction with iodine is the same in all forms of functional hyperplasia. The marked hyperplasias of exophthalmic goiter react exactly in the same way as do the hyperplasias in animals or the hyperplasias of childhood, puberty and pregnancy in man.

In the light of these facts the third view—viz., that active hyperplasia is of constant occurrence at *some* phase in all true cases of exophthalmic goiter but that similar changes occur in *all* developing goiters—is the one most likely to accord with all the facts.

Of 26 cases clinically diagnosed as exophthalmic goiter in which the patients were operated on by Dr. G. W. Crile at Lakeside Hospital 15 had active hyperplasia, varying from colloid-early to marked glandular hyperplasia. Eight had pure colloid goiters. Two had pure colloid goiters containing actively growing fetal adenomata and one had a normal thyroid as regards size, histology and iodine content. With this series one would be inclined to agree with Virchow⁷⁴ when he wrote that the phenomena of exophthalmic goiter depended on neither a distinct variety of goiter, nor a distinct size, nor yet a distinct stage of thyroid change, did we not further inquire into the cases. It was found that the patients with pure colloid goiter had been treated with iodine-containing substances shortly before operation. These cases clinically were quite typical cases of exophthalmic goiter. This finding bears out the observations reported from most of the large clinics that one frequently sees cases of exophthalmic goiter with colloid glands. This, however, means that the thyroid reacts too quickly (three to four weeks) for the clinical manifestations to follow and not that in the progressive stage of the disease there was no active hyperplasia, for we now know that all colloid goiters have been preceded by active hyperplasia. We also know that the histological appearance of the thyroid may change from week to week and there can be little doubt that the varied histological findings reported by all observers is due merely to the stage of the process (regressive or progressive) at the time of the operation. The case in which the thyroid was normal is not unique. There are several reports of such cases. These cases must either be considered errors in diagnosis or that the manifestations were too recent for cell reactions to occur. We are inclined to consider such cases not true exophthalmic

goiter, but rather as severe cases of some clinically closely allied disease like neurasthenia or psychasthenia.

Thus, after carefully reviewing the data, we conclude that thyroid hyperplasia is of constant occurrence at some stage of the disease, but that it also occurs in all developing goiters in all animals.

RELATION OF THE IODIN CONTENT OF THE THYROID TO EXOPHTHALMIC GOITER

The iodine varies inversely with the degree of hyperplasia. We have just seen that the histological structure of the goiters as we obtain them is quite variable; so also is their iodine content. But, just as there is a constant histological change (active hyperplasia) at some phase in all true cases of exophthalmic goiter, so there is a uniform lessening of the iodine content corresponding with the increasing degree of hyperplasia. Oswald⁷⁹ in general found the percentage of iodine lowered in exophthalmic goiter, but he also observed cases in which it was increased. Caro⁸⁰ in a single severe case found the iodine very high. Reinbach⁸¹ could make out no relation between the amount of colloid and the amount of iodine. Kocher⁸² found exophthalmic goiter glands always lower in iodine than normal glands, even to one-thirtieth of the normal.

Two conditions must be fulfilled before one can conclude that iodine bears no relation to exophthalmic goiter: (1) a large series of cases, (2) careful histological comparisons. It seems that this may account for many of the reports in which no relation could be made out, just as it explains why constant anatomical changes were not established earlier. The histology and iodine content for human goiter are modified by so many factors that it is necessary to examine a large series in order to include and allow for variations dependent on the food, medication, age, stage of the disease, etc.

In our 26 cases there was no case in which the iodine did not vary inversely with the histological structure. It was highest in the colloid glands, lowest in the marked hyperplasias, and the highest iodine content associated with hyperplasia was always below the lowest associated with pure colloid gland. We can conclude, therefore, that the iodine content in exophthalmic goiter always varies inversely with the degree of hyperplasia just as in all other forms of active hyperplasia. There are the same difficulties in the interpretation of the anatomical changes. These

79. Oswald: *Virchow's Arch. f. path. Anat.*, 1902, clxix, 444.

80. Caro: *Berl. klin. Wehnschr.*, 1907, xlv, 519.

81. Reinbach: *Centralbl. f. Chir.*, 1898, xxv, 545.

82. Kocher: *Arch. f. klin. Chir.*, 1901, lxiv, 454.

can only be avoided by working with large series and by carefully comparing the iodine content with the histology.

The severity of the cases in general varies with the degree of thyroid and lymphoid hyperplasia. Autopsy and surgical reports from all sources have shown this. In our series there were six patients with marked glandular hyperplasia, of whom four died. Of the four that died three had slight manifestations suggestive of supervening myxedema (dry skin, pigmentation, loss of pubic, axillary and scalp hair, etc.). The ten patients with colloid goiter recovered.

As to the cause of death after operation in these severe cases there are three views: (1) that it is due to the poisoning of the tissues with an excess of thyroid secretion; (2) that it is due to the lymphoid hyperplasia (status lymphaticus); (3) that it is due to true exhaustion of all the tissues, particularly the central nervous system.

The first view embodies the well-known theory of Moebius and Gauthier⁶³ on which the surgical, the cytotoxic and serum treatments rest. Are these hyperplastic glands secreting an increased quantity of physiologically active secretion? If such were the case, the same changes should be produced in the thyroids of animals by feeding with hyperplastic glands as by feeding with normal or colloid glands. This, as is well known, is not true. The physiological activity of such thyroids, as determined by the nitrogen excretion and the histological changes produced in dogs' thyroids, depends on the amount of iodine they contain and the iodine varies inversely with the degree of thyroid hyperplasia. Also, the fact that desiccated sheep's thyroids in large doses (2 to 5 grains three times daily) usually increases the clinical symptoms in proportion to the severity of the case can not be interpreted as proof of physiological hypersecretion, for the reason that the effect of such desiccated thyroid on these patients depends on the quantity of iodine it contains. That this is true can be easily shown by the fact that iodine administered to these cases has (so far as we are able to estimate) the same action as desiccated thyroid. In individuals with normal glands just the opposite of this is true. Iodine in similar doses has no noticeable effect, while desiccated thyroid produces the same manifestations of physiological activity as are shown in cases of exophthalmic goiter, and, also, just as in the exophthalmic goiter cases, the physiological activity depends on the amount of iodine in organic combination. The results of operative treatment according to the hypersecretion theory should be most favorable in those cases with the most active hyperplasia. As a matter of fact, the opposite is true—viz., that the operative mortality is greatest in those cases with the most marked hyperplasia and the lowest iodine contents.

The clinical severity as determined by the symptoms is uncertain, for the reason that the gland may revert to the colloid state with the apparent preservation of the original symptoms. In such cases, as in the cases with slight hyperplasia, the mortality from operation is very low. And, therefore, the mortality, as based on the number of cases clinically diagnosed as exophthalmic goiter, is of little importance. Another view that squeezing or manipulation of the gland produces the marked rise in pulse rate and temperature (so-called hyperthyroidism) by overloading the circulation with the "toxic" secretion has been proved untrue, for the reason that operations elsewhere on the body or injuries, or even mental shock, in this class of cases are with proportionate frequency followed by these symptoms.

The second view that the lymphoid hyperplasia (*status lymphaticus*) is the determining cause of death in these cases has lately been revived and reviewed by Capelle.⁸³ The presence of lymphoid hyperplasia in these severe cases of exophthalmic goiter was perhaps first described by Markham⁶⁸ and later by Marie,⁷⁰ Hektoen,⁷¹ Hansemann¹⁶ and many others. Capelle has found in the collected reports that 44 per cent. of the exophthalmic goiter patients dying of some intercurrent disease; 82 per cent. of those dying directly of the disease and 95 per cent. of those dying after operation had persistent thymus. From these data he concludes that this lymphoid hyperplasia is a separate and complicating condition in exophthalmic goiter. Others look on these changes as part of the essential anatomical lesions in all severe cases. The fact that these same changes are also present in cretin lambs, dogs and children, and also in many cases of adult myxedema, compels us to conclude that it is merely a part of the systemic reaction to the cause or causes producing goiter. We fully agree with Capelle that in all severe cases of exophthalmic goiter there is lymphoid hyperplasia, and also that the mortality is greatest in those cases, but we can not accept his conclusion that the mortality depends on the presence of lymphoid hyperplasia alone. We consider both the thyroid and lymphoid changes as common and the truest indices of the severity of the disease.

The third view is that death is due to exhaustion. This view, it seems to us, more nearly accords with the observed phenomena. All observations go to show that the gland is hyperactive, but that this activity is compensatory in nature. So also all the facts indicate that the quantity of the secretion is increased, but that its physiological activity is decreased. The frequency with which myxedema follows exoph-

83. Capelle: *Beitr. z. klin. Chir.*, 1908, lviii, 353; *München. med. Wehnschr.*, 1908, iv, 1826.

thalmic goiter can not be explained as accidental and, as has been suggested by several authors, is perhaps the greatest objection to the hypersecretion theory. In endemic cretinism, in both man and animals, one notes the same kind of anatomical changes as are observed in exophthalmic goiter, and, as already stated, these changes are common to all developing functional hyperplasias of the thyroid. This is, however, only the anatomical verification of the old clinical phrase that endemic goiter is the first stage of the process leading to cretinism and it seems to us, as Ord³,²⁴ has pointed out, that in myxedema following exophthalmic goiter, we have a very close analogy with cretinism. In this connection it is of great interest to note that Horsley⁶² in his experimental myxedema in monkeys has described a nervous stage followed by the dull listless stage so characteristic of fully developed myxedema, and also that McGarrison,³⁶ in his excellent clinical report on cretinism in the Himalayas, has very carefully described this nervous stage. Whether these anatomical and clinical similarities between the life-history of exophthalmic goiter and of cretinism are closely related or are merely accidental is a problem that is worth very careful study. The nervous symptoms are, however, not common to this disease alone, but may be present in varying degrees in a variety of nervous and mental diseases in individuals with histologically normal thyroids, as in neurasthenia and psychasthenia. The same may be said of the symptoms of extreme tachycardia and high temperature which so frequently follow operations, injuries or mental shocks in these cases. The same phenomena are observed in heat exhaustion. The onset of the disease, while it may be quite sudden, is almost always progressive and preceded by some chronic debilitating disease as typhoid fever, influenza, or by severe mental strain as overwork, anxiety, etc. The whole clinical picture, it seems to us, is one of exhaustion, the seat of which is particularly the central nervous system. Certainly the nervous manifestations predominate and perhaps cloud (at least, by our present standards of interpretation) the true picture of exhaustion. It is difficult to understand why partial removal is so quickly followed by a further hyperplasia of the remaining portion which differs anatomically from the first portion removed in no essential way, and why in spontaneous recovery the gland always returns to the colloid state, unless we assume that the process of hyperplasia of the thyroid is a compensatory one..

In the light of our present knowledge of the anatomy, the chemistry and the biology of thyroid hyperplasia we can not conclude that the thyroid changes in exophthalmic goiter are either primary or specific or that such thyroids are producing an increased amount of a physio-

logically active secretion. On the other hand, we believe that the thyroid changes in exophthalmic goiter are always compensatory or secondary to some more fundamental cause or causes and that there is a hypersecretion quantitatively but a hyposecretion qualitatively (physiologically), and, lastly, that the usual final stage of all cases unless terminated by death or relative recovery is myxedema.

RELATION OF THYROID CHANGES AND IODIN CONTENT TO CRETINISM AND MYXEDEMA

It is now generally accepted that the major disturbance in sporadic and endemic cretinism, in operative myxedema (cachexia strumipriva), and in natural myxedema (Gull's disease) is a lack of thyroid function. This opinion is largely the result of the clinical and anatomical observations from many sources, among which may be mentioned the work of Gull,²³ Kocher,⁸⁴ Ord,⁸⁵ Hun and Prudden,²⁵ Virchow⁸⁶ and Osler⁸⁷; of the experimental observations of Kocher,⁸⁸ Reverdin,⁸⁹ Stokes,⁹⁰ Gordon,⁹¹ Horsley⁹² and Halsted⁹³; of the therapeutic studies by Murray,⁹⁴ Mackenzie⁹⁵ and von Bruns.⁹⁶

So, also, through the work of St. Lager,⁹⁷ Niepce,⁹⁸ Morel,⁹⁹ Hirsch (loc. cit.), McGarrison³⁵ and others, it has been shown that 75 per cent. of all cretins have enlargement of the thyroid clinically, and also that the general relation of goiter to cretinism may be summed up in the words of Morel, that "goiter is the first stage on the road leading to cretinism." From the above generalizations it can be seen that the terms "cretinism" and "myxedema" do not represent simple clinical, anatomical or physiological conditions, but must include all the gradations of the processes of which clinical cretinism and myxedema are the terminal

84. Kocher: *Deutsch. Ztschr. f. Chir.*, 1892, xxxiv, 556.

85. Ord: *Brit. Med. Jour.*, 1888, i, 1162.

86. Virchow: *Die krankhaften Geschwülste*, 1863; *Berl. klin. Wehnschr.*, 1887, xxiv, 121.

87. Osler: *Tr. Cong. Am. Phys. and Surg.*, 1897, iv, 169.

88. Kocher: *Arch. f. klin. Chir.*, 1883, xxix, 254.

89. Reverdin: *Rev. méd. de la Suisse rom.*, 1882, 539.

90. Stokes: *Brit. Med. Jour.*, 1886, ii, 709.

91. Gordon: *Lancet*, London, 1886, ii, 65.

92. Horsley: *Lancet*, London, 1884, ii, 1133.

93. Halsted: *Jour. Exper. Med.*, 1909, xi, 175.

94. Murray: *Lancet*, London, 1893, i, 1130.

95. Mackenzie: *Lancet*, London, 1893, i, 123.

96. Von Bruns: *Beitr. z. klin. Chir.*, 1896, xvi, 521; 1894, xii, 847.

97. St. Lager: *Etudes sur les causes du crétinisme, etc.*, Paris, 1867.

98. Niepce: *Traite du goitre et du crétinisme*. Paris, 1851, i.

99. Morel: *Du goitre et du crétinisme, etc.* Paris, 1864.

stages. The intermediate stages are best indicated by the various degrees of active thyroid hyperplasia and in an earlier paper one of us (Marine⁴) suggested the borrowed term "cretinoid" (Gull²³) as the best descriptive word for the several degrees of hyperplasia seen in dogs, sheep, ox, pig, and human thyroids, since the greater number of these animals having active hyperplasia have no detectable clinical manifestations.

The anatomical changes usually present in typical cretin animals are characterized by the extensive overgrowth of fibrous tissue resulting from the dying off of the epithelial cells. We have not found any definite anatomical descriptions of glands in the early stages of this fibrous tissue replacement of the epithelial hyperplasia. It has been our fortune to observe five cretin puppies and two cretin lambs in which these changes were occurring. As previously mentioned (under anatomical descriptions), the epithelial cells at first enlarge and the nuclei become hyperchromatic. Later these cells become irregular in size and shape and the normally regular outline of the vesicular epithelium is broken. The increased connective tissue crowds out these degenerated cells and finally the vesicle, much reduced in size, becomes filled with the irregular cell masses and the detritus of the more degenerated cells. These changes have been observed only in thyroids of lower animals with clinical manifestations of cretinism. Of perhaps greater interest is the fact that similar disturbances in the nucleus-plasma relations of the epithelial cells have been observed in four cases of exophthalmic goiter which clinically showed manifestations of myxedema.

When these anatomical changes and their clinical associations with cretinism and myxedema are considered together they suggest that the further ability of the cells to grow and divide normally has been seriously disturbed and that the major factors in this disturbance are overwork and lack of proper nutrition, as was pointed out by Popoff¹⁰⁰ for protozoan cells. In cretin puppies we have been able, by the administration of iodine, to make these cells revert to the flattened cubical form, while the gland as a whole returned to the colloid or resting condition, and later by partial removal to produce a perfectly regular and uniform hyperplasia in the same gland. Professor Howard and Dr. Schultz, to whom we have referred these observations, are of the opinion that these thyroid changes, consisting in the production of depression and the recovery therefrom, are comparable to the protozoan cell changes described by Hertwig and his pupils. The most suggestive explanation at present seems to be that these degenerative and atrophic cell changes are the

100. Popoff: Arch. f. Protistenk. (Suppl.) Festband f. R. Hertwig, 1907, p. 43.

result of prolonged and unrelieved physiological stimulation to meet some deficiency, and that cretinism and myxedema are the final stages of the failure in compensation.

In view of what has been said above, the earlier statement that in cretinism and myxedema there is a lack of thyroid function is somewhat misleading because the thyroid in the early stages of the process is hyperactive, while, at the same time, the body as a whole suffers from a lack of normal function. Thus it would appear that in the cretinoid and in the myxedematous process the real deficiency lies in the physiological value of the thyroid secretion to the organism. This deficiency may be produced either by atrophy or absence of the gland, or by the absence of the normal elements of nutrition with which the normal metabolic activities of the gland are concerned. Iodin is perhaps one of these elementary deficiencies.

In the true cretin the gland histologically presents marked overgrowth of fibrous tissue, with a corresponding disappearance of the epithelial elements, while in the preclinical stage the gland presents a marked epithelial hyperplasia with relatively slight increase in the supporting fibrous tissue. Thus with the progressive epithelial hyperplasia finally giving way to the fibrous overgrowth as typifying the anatomical changes in the cretin or myxedema thyroid, it may be said that the symptom-complex varies with the degree of epithelial hyperplasia and fibrotic atrophy.

As regards the iodine content in human cretin thyroids no specific observations are recorded. In the five cretin dogs examined by us we could find no trace of iodine, and in the four cases of exophthalmic goiter showing clinical signs of myxedema the highest iodine content was 0.544 and the lowest 0.118 mgm. per gram of dried gland. This suggests that the iodine content varies inversely with the degree of hyperplasia and fibrosis in both cretin and myxedema glands. With the exception of tumors and infants' thyroids, these were the lowest iodine contents observed. There are variations and modifications in the iodine content and histologic structure of cretin and myxedema glands in man that are comparable to the variations above noted in other clinical varieties of goiter, and depend on the age of the individual, previous medication, the presence of complicating and degenerative changes, etc. These variations and modifications we believe could be easily explained if the life-history of such patients could be accurately ascertained. But, as this at present is quite impossible, our hope lies in the accumulation of sufficient cases to include all the variations and the essential types of change as well.

In conclusion we believe that the various degrees of thyroid hyperplasia are but stages in a common process the final result of which is cretinism or myxedema and that the percentage of iodine varies inversely with the degree of hyperplasia and fibrosis.

CONCLUSIONS

1. Active thyroid hyperplasia is present in all developing goiters in all animals.

2. All thyroid hyperplasia, so far as we can determine, is anatomically, chemically (iodine) and biologically the same.

3. Thyroid hyperplasia develops in both normal and colloid glands.

4. Colloid glands, anatomically, chemically and biologically, are the nearest approach to the normal gland that hyperplasias can become and obey all the known biological laws of normal glands in so far as these laws are at present known.

6. The various degenerations, hemorrhages and cysts are secondary and complicating changes engrafted on to the three fundamental types of normal, hyperplastic and colloid glands.

7. Iodine is necessary for normal thyroid activity.

8. The iodine content varies inversely with the degree of hyperplasia.

9. The percentage of iodine present in thyroids is variable, but there is a quite constant minimum percentage necessary for the maintenance of normal or colloid gland structure.

10. Iodine is taken up rapidly by the thyroid, the rapidity depending on the degree of active hyperplasia.

11. Mild degrees of thyroid hyperplasia accompany or follow many of the chronic nutritional disturbances without detectable clinical symptoms referable to the thyroid.

12. Exophthalmic goiter is constantly accompanied during the progressive stage of the disease by thyroid hyperplasia and the iodine percentage varies inversely with the degree of hyperplasia.

13. In endemic cretinism the fibrous overgrowth with atrophy of the gland cells is consequent on active hyperplasia and is associated with a very low iodine content.

14. In myxedema the anatomical and iodine changes are similar to those of cretinism.

We wish to acknowledge our indebtedness to Prof. W. T. Howard for the anatomical material; to Prof. G. W. Crile for his surgical material at Lakeside Hospital, and also to thank Professors Howard and G. N. Stewart for their careful criticisms and suggestions.

Reprinted from The Archives of Internal Medicine
November, 1909, Vol. 4, pp. 440-493

AMERICAN MEDICAL ASSOCIATION
FIVE HUNDRED AND THIRTY-FIVE DEARBORN AVENUE
CHICAGO

A CASE OF GENERAL INFECTION WITH *BACILLUS MUCOSUS CAPSULATUS* FOLLOWED BY AN AREOLAR ABSCESS OF THE LIVER AND GENERAL PERITONITIS. AUTOPSY.

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Primary idiopathic abscess of the liver, except in cases of [77] direct or indirect traumatism, may be said very seldom to occur. In direct traumatism a penetrating dagger, a splinter of wood, a bullet or the like, may carry in with it infecting organisms and suppuration may follow. In indirect traumatism, as by a blow or fall on the hepatic region, the liver may receive severe injury, some of its blood vessels may be ruptured, hæmorrhage may take place into the parenchyma, and the resistance of the organ be greatly lowered. It may form as a result of such injury a fertile soil for the growth and multiplication of organisms, which would otherwise not be attracted to it, or whose virulence normal liver tissue could readily withstand. In all other cases of hepatic abscess we must, ordinarily, consider the condition secondary to a focus in some other region of the body. The source of infection may be at times comparatively small, insignificant, and easily overlooked. Josserrand (1) has reported a case of amœbic abscess of the liver occurring ten years after an attack of dysentery. In such a case the infectious focus must be of the nature of a chronic inflammation. The amœba must have been lurking and living in some portion of the body and there producing a certain amount of irritation, though not enough, perhaps, to produce any manifestly discernible symptoms. However, there are cases

[77]on record (2) of undoubted abscess of the liver, in which amœbæ were found in the abscess, but no history of preceding dysentery could be obtained, and in which post-mortem examination showed a normal gastro-intestinal tract. There is, also, recognized by some authors (3) a group of cases of infective suppurative hepatitis with abscess formation in which the utmost care has failed to reveal, either during life or after death, any primary point of infection.

The clinical history of our case is as follows, and seems to belong to the above described third group :

A. J., white, American, æt. 23, married, book-keeper, entered hospital April 30, 1908.

Complaint.—Fever and abdominal pain.

Family History.—Unimportant.

Personal History.—Unimportant.

Present Illness.—Patient has not felt like work for the past ten days. Four days before admission to the hospital he was seized with fever, which has persisted without remission. The next night he had irregular fleeting pains in the upper right chest and a dull constant pain in the upper right abdomen and back. He also had headache and a feeling of chilliness. He vomited frequently that night, but has not vomited since. On the day before admission he had a severe chill. He has never been jaundiced.

Physical Examination.—On admission, temperature, 103.4° F.; pulse, 92; respirations, 22 to the minute.

Patient is fairly well developed and rather poorly nourished. Face is flushed. Herpes on lips. Tongue is dry and coated with a white fur. The superficial lymph glands are not enlarged.

Thorax.—Normal.

Abdomen.—Liver extends from the 4th rib above to 2.5 cm. below the costal margin. Its edges are not palpable. Palpation is very painful over the right lobe of the liver, but less so over the left lobe. Deep palpation is slightly painful in the right iliac region. Abdomen is not distended. Spleen apparently enlarged, palpable just below the costal border.

May 2.—Epigastric pain, which has been very severe, has now markedly decreased. His abdomen is quite distended, especially below the umbilicus.

Operation.—Exploratory laparotomy and drainage by Dr. D. P. Allen.

On opening the abdomen the liver seemed somewhat enlarged. The hepatic flexure of the colon was drawn up and found covered with fibrino-purulent exudate. The cæcum and appendix were exposed; the latter was free and not enlarged; its peritoneal sur-

face was dull and partially covered with seropurulent material. [77] The pelvis was explored and found full of thick yellowish pus. The peritoneal coat of the small intestine was found injected and quite dull in appearance. No perforation could be found. Owing to the patient's poor condition it was thought unwise to attempt further to discover the source of the pus.

May 5.—On the day following the operation, May 3, the patient looked brighter and his general condition had improved. Late in the afternoon of May 4, his temperature began to rise and he became restless. During the following night his pulse became weak and rapid; by morning it was weaker and more rapid; he was at times delirious, and died at 8.15 p. m.

Urine.—At no time, either before or after operation, did the urine show anything of importance.

On May 4, the day before the patient died, a blood culture taken, under aseptic precautions, from the median basilic vein of the right arm gave the *B. mucosus capsulatus* in pure culture. Its appearance and general characteristics, as well as its cultural growth, were identical with the organism obtained at autopsy and described in the bacteriological report of this paper.

Autopsy, 938.

[78]

May 6.—13 hours after death.

Anatomical Diagnosis.—*Acute, general, diffuse, fibrino-purulent peritonitis; areolar abscess of liver; general infection with B. mucosus capsulatus; parenchymatous degeneration of the heart muscle, liver, kidney, adrenal and pancreas; acute lymphadenitis; acute splenic tumor; edema and congestion of lungs.*

Abdominal Cavity.—The abdominal wall is quite thin; the subcutaneous fat scanty. The serous surface of the abdominal wall and viscera is everywhere covered with a layer of thick greyish-white purulent material of very foul odor. Beneath this exudate the surface is deeply injected and dulled. The inner surface of the abdominal wound is quite ragged, its margins ulcerated and covered with fibrino-purulent exudate. The omentum is massed on itself and drawn over to the left hypochondriac region. It is matted together by fibrino-purulent adhesions and its surfaces, with the serous surfaces in general, are covered with fibrino-purulent exudate. All the abdominal fossæ and dependent portions of the cavity are filled with soft creamy pus. The appendix is free, short, straight and firm. Its tip lies over the brim of the pelvis in a pool of pus.

The liver reaches 10 cm. below the costal margin. The surfaces of both lobes are covered with fibrino-purulent exudate. This may be stripped off in sheets from the upper surface. The surface is deeply congested and red. On passing the hand upwards between the diaphragm and the liver, the liver substance readily yields to

[78] pressure and there is distinct fluctuation. The gall-bladder, filled with bile, appears normal.

The spleen is enlarged and soft. It is adherent to the diaphragm, fundus of the stomach, and abdominal wall by delicate fibrino-purulent adhesions.

Examination of the whole alimentary tract, from the œsophageal opening of the stomach to the anus, shows no perforation.

Liver.—It weighs 2000 gr. It measures 25 x 22 x 9 cm. Its peritoneal surface is everywhere covered with a membrane-like layer of fibrino-purulent exudate. Beneath this membrane, which may be readily stripped off in sheets, the liver surface of the left lobe appears of a fairly uniform light greyish-yellow color. The surface of the right lobe shows marked mottling, especially over its posterior portion. Over this region of the right lobe the surface is of a general dark red color, dotted at several points with irregularly quadrilateral and round, opaque, soft areas, varying from 1-2 cm. in diameter. Over these opaque areas the surface is roughened and in some places broken. Where they are broken they are seen to open into subjacent abscess cavities. The anterior portion of the right lobe is fairly soft and friable; the posterior portion, quite soft and fluctuating. On pressure, greyish-white, foul-smelling, purulent material may be pressed out through the openings on its surface. Beginning at a point on the outer border, 5 cm. from its anterior extremity, there is an irregularly triangular area, measuring 10 x 8 cm., throughout which the liver surface is deeply injected and of a dark red color. At its base it merges into the abscess area in the posterior portion of the lobe. On section the cut surface of the anterior portion of the right lobe and the whole of the left lobe have, practically, the same appearance. It is of a pinkish-yellow color, soft and friable. The lobules are readily made out and the central veins are visible as small, injected, red points. The central veins are surrounded by an ill-defined ring of light yellowish-grey tissue, slightly translucent. Outside of this the tissue of the portal spaces is darker and more opaque. Section through the triangular area described above, shows a cut surface of deep red color and slightly mottled. The tissue is of a softer consistency than that in the anterior portion of the lobe. The lobules are very indistinct and ill-defined. The blood vessels are distended and filled with greyish-red, fairly firm thrombi. Scattered over this area, increasing in number as we proceed posteriorly and towards the outer border, there are numerous greyish-white points, varying in size from a pin point to 1 cm. in diameter, and from which on pressure soft tenacious opaque material may be expressed. These points can be readily seen to be situated in the hepatic veins.

The Abscess.—A section through the posterior portion of the

right lobe shows an irregular ellipsoid area, measuring 10 x 9 x 7 [78] cm., with a fairly well-defined border separating it from the surrounding deeply congested liver tissue. Over this area the tissue is seen to be made up of a network of intercommunicating sinuses and alveolar spaces, filled with greyish-white, foul-smelling, tenacious and viscid purulent material. The intervening septa of liver substance have a slightly tortuous radial arrangement. The veins contain deep red and reddish-white thrombi. On opening the inferior vena cava a thrombus is found projecting for a distance of 1 mm. from the main hepatic vein. On pressure purulent material may be expressed from the hepatic veins into the lumen of the inferior vena cava.

The portal vein, when examined throughout its course and as far into the liver substance as its branches can be readily followed, is everywhere free and shows no thrombi, emboli or evidence of pylephlebitis.

MICROSCOPICAL EXAMINATION.

Liver.—Examination of the abscess area shows the abscesses to have a fairly uniform structure. Proceeding from the center of one of the abscesses towards the periphery, we meet, first, a vacuolated, pink-staining area of necrotic structureless material; outside of this area there is a darker zone of densely packed and deeply staining leucocytes, small round cells, broken liver cells and granular material; along the outer border of this zone there is an irregular line of bacilli; outside of this line we have the degenerated cells of the liver parenchyma and of the septa that run between the abscesses. These septa vary in width. Scattered through them are numerous areas of small hæmorrhages. The bile ducts are well preserved and are undergoing active hyperplasia. Beneath Glisson's capsule there is a zone of round cell and leucocytic infiltration. The blood vessels are dilated and distended with blood.

Sections from the anterior portion of the right lobe, just anterior to the abscess area, show numerous small and large solitary abscesses, which appear as local areas of suppurative phlebitis, always associated with a hepatic vein. The lumen of the vein is filled with polymorphonuclear leucocytes, small round cells, broken endothelial cells and granular material. Bordering on and in the wall of the vessel are numerous bacilli, often aggregated in clusters. In the large areas the wall of the vein has been almost destroyed and exists only as a ring of degenerated connective tissue cells; in the smaller areas it is fairly well preserved. Outside of the vessel wall there is a band of broken liver cells and marked leucocytic and small round cell infiltration. In the very smallest abscesses the suppuration is limited almost entirely to the lumen of the vessel.

- [78] In the remaining portion of the right lobe and throughout the left lobe there is only acute congestion of the blood vessels and parenchymatous degeneration of the liver cells. The connective tissue about the portal spaces is slightly increased and there is round cell infiltration. There is nowhere any evidence of an acute cholangitis, either in the small or large bile ducts.

BACTERIOLOGICAL REPORT.

Smears were made from the fibrino-purulent peritoneal exudate and from the purulent material obtained from the large liver abscess. The bacteriological picture is identical in both preparations. With the gentian violet stain there is seen a large plump bacillus, varying in length from $3.8\ \mu$, with rounded ends and a distinct halo about each organism. With Welch's capsule stain distinct capsules can be made out about each organism. No other organisms could be seen. No amœbæ or other protozoan organisms were found in the liver abscesses. The organism found decolorized with Gram's stain.

Cultures made on plain agar from the heart's blood, liver, spleen, lung, and kidney were positive in all save those from the spleen. The cultures in all were pure and their growths identical.

The organism obtained from the cultures is about $.5\ \mu$ in width, has rounded ends and varies from $3.5\ \mu$ in length. It decolorizes with Gram's stain, has no spores, and is non-motile. After 24 hours incubation at 37°C ., its cultural growths are as follows:

Plain Agar.—There is an elevated white lustrous growth with wavy margins. When touched with a platinum needle it is seen to be very tenacious and mucus-like. Subsequent growth showed no marked change.

Glucose Agar.—Stab cultures showed marked gas formation, portions of the media are raised 1 cm. above adjacent portions.

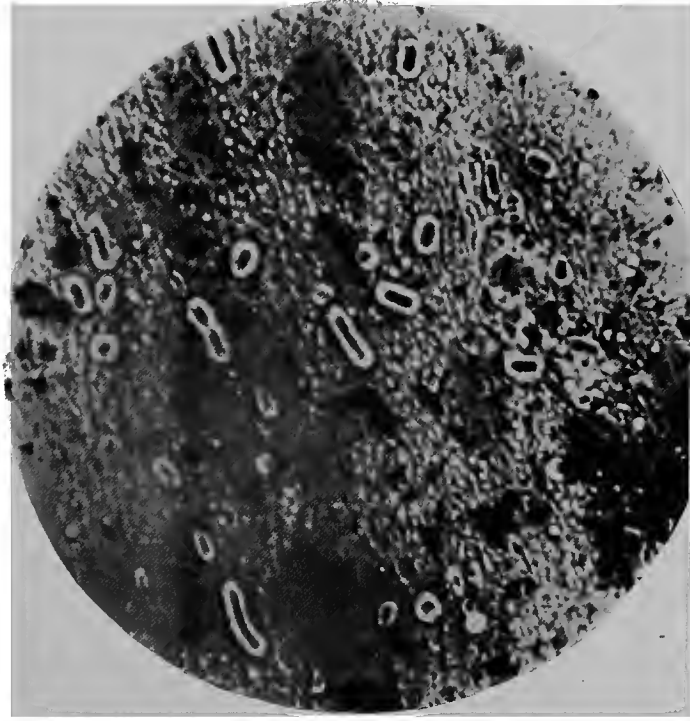
Litmus Milk.—There is coagulation and acidification. Cover slip preparations stained with Welch's capsule stain showed distinct capsules. Subsequent growth showed no peptonization.

Plain Bouillon.—There is a diffuse turbidity and slight greyish-white sediment. Subsequently the turbidity greatly increased and a distinct pellicle formed.

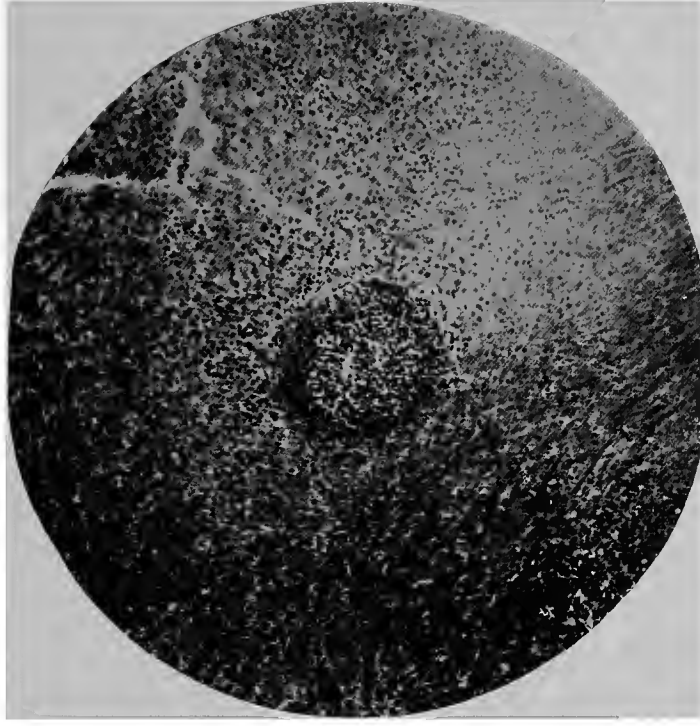
Potato.—There is a rather diffuse greyish-white growth, quite moist and viscid, with marked gas formation in the water of condensation along the side of the tube.

Dunham's Bouillon.—There is a growth similar to that noted in the plain bouillon. After 12 days there is a fairly marked indol reaction with 10 per cent sulphuric acid and 1 per cent sodium nitrite.

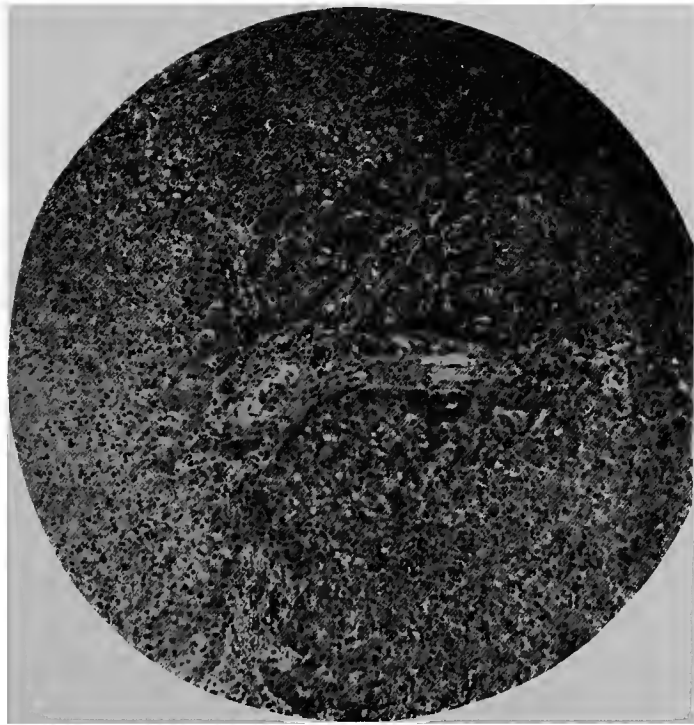
Gelatin.—After 3 days growth at room temperature (about 20°C .), there is a distinct growth along the stab and an accumulated growth on the surface, giving a nail-head appearance. There is



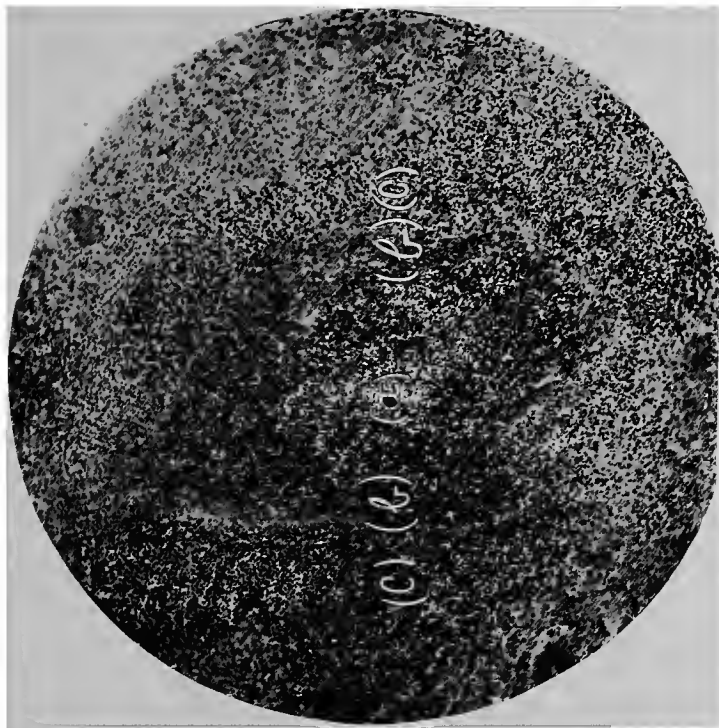
A smear from one of the liver abscess cavities, stained with Welch's capsule stain. A smear from the peritoneal exudate, stained in the same manner, shows a similar picture. $\times 1000$.



One of the smallest vessels, showing the lumen of the hepatic vein filled with purulent material and the leucocytic infiltration almost entirely limited to the vessel wall. $\times 100$.



A portal space, showing nothing abnormal, save a slight round cell infiltration and slight increase in the connective tissue. $\times 100$.



A section of one of the smaller abscesses situated just anterior to the large areolar abscess showing (a) the lumen of a hepatic vein filled with purulent material, (b) the ill-defined vessel wall, and (c) the marked leucocytic infiltration around the margin of the vessel. $\times 100$.



no gas formation or liquefaction. Subsequent growth showed no [79] change.

Blood-serum.—There is a lustrous white growth along the line of stroke. It is very tenacious and stringy when touched with a platinum needle. Its margins are wavy.

Animal Inoculation.—1 cc. of an emulsion, made from a 24-hour growth on slant agar with sterile bouillon, injected subcutaneously over the abdomen, produced death in a guinea-pig in 27 hours. At autopsy the organs were found generally congested and moist; the lungs, œdematous. Cultures made on slant agar from the heart's blood, lung, liver, spleen, and kidney, in each tube, gave a pure culture of an organism, in all particulars, similar to the one described above.

Anærobic cultures, grown in air-tight jars deoxygenated with pyrogalic acid and sodium hydroxide, showed a growth quite similar to that obtained aerobically, save that it grew much slower and not so luxuriantly.

The fermentative power of this organism was tested in no other media than glucose agar. The activity of the fermentation there noted and the fact that it acidified and coagulated litmus milk, make it most probably belong to the "ærogenes" group of the capsulated bacilli, as described by Strong (4). Moreover, Perkins (10) has shown that all of the aerobic capsulated bacilli that have the power to break up sugars with gas formation may, by change of environment or passing through animals, be reverted to the "ærogenes" group as the prototype; that these organisms may, also, lose their fermentative power, in whole or in part, through modifications in environment.¹

The clinical history, autopsy, and bacteriological findings in this case are extremely interesting in as much as a case of general infection and gas-cyst formation in man (5), an epizootic infection of the laboratory guinea-pigs (6), both due to the *B. mucosus capsulatus*, and a study of the group of capsulated bacilli, in which organisms of the *Bacillus mucosus* type were noted 56 times in 74 consecutive autopsies (11), have already been reported from this laboratory, and we are, still, repeatedly meeting with this organism as a primary and secondary invader in various kinds of lesions and conditions found at autopsies.

In the case here reported we apparently had first a gen-

¹ Only that portion of the autopsy and microscopical findings have been described here which bear directly on the case.

[79] eral bacteriaemia and septicæmia, due to the *B. mucosus capsulatus*; subsequently, there was the formation of numerous minute abscesses in the liver. These minute abscesses increased in size till portions of their peripheries became coalescent, and thus formed the large multilocular, areolar abscess; this extended to the peritoneal surface of the liver, from which the infection spread to the general peritoneal cavity.

One of the series of cases of general septicæmia reported by Duval and Lewis (7) is important in this connection. A male patient, 37 years of age, born in Holland, and a cigarmaker by occupation, came into the hospital complaining of general malaise, loss of strength, and fever. He remained in the hospital 5 weeks, recovered completely, and returned to work well and strong. On the day after admission a blood culture was taken, under aseptic precautions, and plates yielded a pure culture of *B. capsulatus*. There were from 50 to 200 colonies per plate. One week after admission a second blood culture was taken. The cultures again were pure and showed the same organism. The number of colonies to the plate was larger than that obtained from the first cultures. A third blood culture was taken on the day of discharge. Again the cultures were pure and the number larger than that noted at any time before, equal and the same quantities of blood having been plated at each time. They note the apparent rarity of this organism as an agent of general infection and believe that the conclusions of this case have important bearings on immunity problems.

At the time the patient was discharged there were more bacteria circulating in his blood than when admitted to the hospital, as shown by bacteriological cultures; still he was to himself and others well and able to do work. Two weeks after his discharge the patient was seen at work and feeling perfectly well. These facts, they argue, indicate that, in addition to the acquired immunity to soluble toxins and the acquired bactericidal immunity, the human body has other mechanisms of protection against bacterial infection. The tissues in this case, they think, seem to have acquired a resistance to the toxic products of the infecting organism without there being de-

veloped substances harmful to the bacterial cell, the resulting condition becoming possible by the survival of the host and being a causal one between the animal body and the bacterium. [79]

Perhaps this explanation, in a measure, offers a solution of the conditions of our case. Here the liver may be considered to have lost this power of resistance to the infecting organism and consequently suppuration and abscess formation has resulted.

Why the liver or any organ should lose this power of resistance and become the focus of infection and the other organs remain free, while infectious organisms are continually circulating through them, has been a recognized but unsolved problem for years. [80]

As to why the abscesses should, in the present case, be exclusively connected with the hepatic veins is also quite difficult to answer. There would appear to be no reason for or evidence of retrograde embolism. There were no thrombi in the heart or thoracic vessels; special care was taken to look for them.

This type of abscess is also rather interesting. It was first described by Charcot under the name "abcès aréolaire" (8) in connection with suppurative cholangitis and by Chauffard (9) in connection with suppuration in the portal system. It has also been described in connection with suppurative phlebitis of the hepatic veins. It is characterized by its infarct-like form and spongy structure. It may be formed by the fusion of numerous points of suppuration about the radicles of the portal or hepatic vein, or the branches of the hepatic bile ducts. A pyogenic membrane may form around its periphery and ultimately a well defined capsule may develop. It is said to be most commonly associated with infections of the appendix.

In conclusion we may safely say from the evidence here given, that—

1. *B. mucosus capsulatus* may form multiple abscesses in the liver. These may be of the areolar type and result from a general infection with this organism, where the mode of infection and the point of inoculation is not apparent.

2. These abscesses may be all associated with the central

[80] hepatic veins of the liver lobule, for some reason and by some process that we are not able to determine.

I am greatly indebted to Dr. W. T. Howard for aid and assistance in the preparation of this report and also to Dr. David Marine, of the Western Reserve Medical School, for the accompanying microphotographs.

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PARAPSORIASIS: A RESISTANT MACULO-PAPULAR
SCALY ERYTHRODERMIA, WITH A REPORT OF
THREE CASES, TOGETHER WITH PATHOLOG-
ICAL HISTOLOGY.

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AS in other types of cutaneous disease, cases of anomalous or apparently hybrid scaly eruptions have been from time to time encountered. Lailler in 1871 observed a scaly eruption which he regarded as pityriasis rubra, and of which Baretta made a model for the museum of the Hôpital St. Louis. A duplicate placed in the Royal College of Surgeons of England was labeled by Sir Erasmus Wilson, in 1873, "lichen planus retiformis." This model has since been identified by Radcliffe Crocker as belonging to the group of dermatoses which forms the title of this paper.¹ It was not, however, until Unna, in connection with Santi and Pollitzer, published a description of two cases in 1890,² under the name of parakeratosis variegata, that the subject attracted special attention. The next to make note of this condition were Jadassohn (*eigen-artiges psoriasiformes und lichenoides Exanthem*, *Dermatitis psoriasiformis nodularis*) and Neisser (*psoriasiformem und lichenoidem Exanthem*), who presented cases before the Deutsche Dermatologische Congress in 1894, which have been recognized as belonging to this group.³ With Brocq's description of what he termed "erythrodermie pityriasiqne en plaques disséminées" in 1897,⁴ there soon appeared a number of cases reported by observers in different countries, which, while presenting certain differences, are now thought to belong to the same group—if not forming a distinct affection. The same year Juliusberg reported a case of "Pityriasis lichenoides chronica,"⁵ while Pinkus⁶ and Róna⁷ followed with reports of similar cases.

Read before the 32nd Annual Meeting of the American Dermatological Association, Annapolis, September 25, 1908.

A year later Eudlitz⁸ presented a child before the Société Française de Dermatologie, with an eruption of four months' standing, which he called "Psoriasis en gouttes d'aspect syphiloïde." Brocq includes this case in the type parapsoriasis, a term he has since proposed for this disease. In Great Britain, Jamieson exhibited three cases of a unique scaly exanthem before the British Medical Association in 1898, two of which Unna regarded as indubitable examples of parakeratosis variegata.⁹ The first to make note of this condition in America was J. C. White, who reported two cases before this association in 1900,¹⁰ which he regarded as counterparts of those described by Brocq. In 1901 Radcliffe-Crocker published a report of two cases, presented before the Dermatological Society of London, which he called "Lichen variegatus."¹¹ Ravogli,¹² in 1901, reported what is probably the third American case, in a child three years of age, under the name "Erythroderma squamosum." A case was likewise reported by Casoli¹³ in Italy at this time, which Brocq includes in *les parapsoriasis*. Later in the same year (1901) a case of parakeratosis variegata was reported by T. Colcott Fox and J. M. H. Macleod,¹⁴ who gave an exhaustive analysis of the cases thus far recorded, and drew the conclusion that while the cases collected presented certain minor variations, yet the more distinctive features were well defined and constant, which entitled them to be classed as a separate affection, for which they proposed the provisional name of Resistant Maculo-Papular Scaly Erythrodermias.

More recently, 1903, C. J. White¹⁵ reported the third case seen in Boston, and entered more at length into the etiology of the condition.

In this connection I wish to report three cases observed during the past year, which, I believe, answer in the main to the descriptions of the cases, under various names, cited above.

CASE 1.—V. T. A., male, aged 25, American, school teacher. Presented himself November 11, 1907, with a scaly eruption which covered nearly the whole body.

Family History: His mother is said to have died of "dropsy" following "asthma," at the age of 57. Father still living and enjoys good health. The only disease the father can recall is that of "boils" observed several years ago, which were supposed to be occasioned by scratches in trimming a

hedge. The patient has two brothers older than himself who have always been well.

Previous Condition: The patient has likewise enjoyed good general health all his life; although being troubled sometimes in summer by a slight looseness of the bowels. The present disease began five years ago: first appearing during the winter, and was most noticeable on the trunk, although to a less extent the extremities were likewise involved. During the first year or two the eruption almost completely disappeared during the summer months. After the second winter, however, it became permanent and more marked, or "thickened," as he expressed it. He has observed during the summer that the parts exposed to the sun, viz., the forearms, have a tendency to recover their normal condition, and he believes that copious perspiration has likewise beneficent effect. The face, hands, scalp and feet have been almost entirely free.

Present Condition: Patient is strong, robust, is florid, and weighs 202 pounds; height, 5 feet 9 inches. His teeth are sound, one having been removed. The mucous surfaces of the pharynx and buccal cavity are normal, with the exception that the former is slightly congested, which the patient attributes to a "cold." The superficial lymphatic glands are palpable. Nearly the whole surface of the body is covered with a reddish papulo-squamous eruption, most marked on the trunk and proximal end of the extremities. The only parts that enjoy immunity are the face, scalp, hands and feet. On the parts first mentioned, nearly the whole cutaneous surface is involved with pea to dime-sized maculæ, varying from a yellowish to dusky red color. Most of these lesions are covered with a few loosely adherent scales. Here and there large papillæ are seen, of a more pronounced dark color, about the size of a lentil, flattened at the apex, some of which are covered with light yellowish scales of varying thickness. The color of the eruption is therefore not uniform, and is deeper and of a bluish-red tint on the lower part of the trunk. Intervening between the lesions are small areas of normal skin, giving to the whole surface a somewhat variegated or reticulated appearance. On scratching, the denuded area does not show hæmorrhagic puncta. The subjective symptoms are for the most part negative, although the patient says when heated a slight itchiness is sometimes felt.

The case was regarded as an anomalous form of psoriasis of the guttate variety with the abortive formation of scales, and appeared to be quite amenable to treatment.

He was given an ointment composed of salicylic acid and tar; in short, the ordinary treatment for mild cases of psoriasis.

He returned at the end of the month with but slight improvement, and upon further examination it was apparent that the eruption was not a simple psoriasis, but corresponded to Brocq's description of "*les parapsoriasis*."¹⁶ Since which time, the patient has been under observation and has been given a trial of arsenic internally, as well as various preparations to be applied to the skin, without, so far as I am able to ascertain, any marked improvement.

In June, 1908, the case was presented to the dermatological section of the American Medical Association at its meeting in Chicago.

Some members present of wide experience promptly pronounced it a case of psoriasis, while others recognized it as belonging to the rare group of scaly eruptions previously described under various names.

It was suggested, by way of treatment, that mild or soothing applications be made, such as the glyceride of starch and zinc. A letter from the patient a few days ago tells me that the mild applications, he thinks, are less effective than the stronger ones at first used.

Soon after this case was first seen, another came under observation, of a more decidedly psoriatic appearance, and without the papules, which were a prominent feature in the case above described. Were it not for the published cases of Brocq's group of *les parapsoriasis* before me, the case next to be described would have been classed as psoriasis, notwithstanding it was somewhat allied in appearance to seborrheic eczema.

CASE 2.—B. V., female, aged 33, Italian, presented herself with a scaly eruption. Nothing worthy of note could be elicited from the family history.

The previous history of the patient showed that she had been married thirteen years, and had four children all of whom are still living and well. She had had a skin disease ten years ago, which she said was dry and scaly. It remained three

or four years, after which she was free until two years ago, when the present eruption came.

Present Condition: The patient is well nourished and appears unusually strong. The eruption is symmetrically distributed and seems to be almost wholly confined to the extremities. It is most abundant on the flexor surface of the middle third of the arms and to a less extent on the corresponding position of the legs. There is a slight mottling of the face over the malar bones, suggesting the so-called butterfly-shaped lupus erythematosus. The lesions are macular, varying from a pinkish to a fawn color, dry, scantily covered with scales, and are roundish or oval in shape. In some instances they coalesce forming larger plaques. In the central area of some of the plaques the eruption is less marked as if resolution were taking place. The disease has not invaded the scalp, nor has it appeared to a noticeable extent on the face, hands or feet. The eruption has always been dry and there is slight itching only when the patient becomes warm. At other times there are no subjective symptoms. The mucous membranes are not involved and no enlargement of the superficial lymphatic glands can be detected.

The treatment consisted of that usually employed in psoriasis, but was followed by no perceptible improvement.

The case is still under observation.

CASE 3.—F. H., male, aged 52, native American, farmer by occupation, entered the surgical ward of Lakeside Hospital complaining of a painful affection of the neck, which the skiagraph showed to be a slight enlargement or exostosis of the right lateral process of the second cervical vertebra. While awaiting an operation for the relief of this affection, a peculiar mottled, or variegated papulo-scaly eruption was noted.

The family history is negative.

The previous history showed that he had always enjoyed good health until about a year ago when he noticed pains in the neck which have continued and for which he seeks relief. The patient says the present eruption began about three months ago, but as it was unaccompanied by subjective symptoms, the exact time of its appearance could not be given.

Present Condition: The patient is a spare, tall man,

slightly anaemic, although enjoying fair health. The eruption came without apparent cause, is symmetrically and widely distributed, most marked on the trunk and extremities, but one or two spots are also seen on the hands, while the face, scalp and feet remain comparatively free. There is one small reddish pin-head sized lesion on the palm of one hand. On the trunk and proximal portion of the extremities the eruption is well marked, consisting of maculae of a pinkish-fawn color, dry and slightly scaly, together with a sprinkling of reddish papules about the size of lentils or small peas. The first glance suggested a luetic eruption, but on further inspecting different parts of the body, this was found untenable. The mucous membranes were not involved, excepting a slight congestion of the pharynx. There was a marked enlargement of the superficial lymphatic glands. The skin disease seemed to be an exact counterpart of the first case herein reported. With the failure of therapeutic measures previously adopted and thinking, possibly, mercury might cause absorption of the exostosis, intramuscular injections of mercury bichloride were given for nearly ten days. As no perceptible amelioration followed at the end of this time, and as the patient was desirous of returning home, an operation for the removal of the exostosis was performed by Dr. G. W. Crile and all other treatment discontinued. During the few weeks at the hospital no perceptible change could be observed and the patient returned to his home in Illinois, relieved of the cervical pains but with the eruption unchanged.

Clinically, cases number one and three are identical, and correspond to the papulo-scaly eruptions described by Unna, Jadassohn, Neisser, Pinkus, Róna, Eudlitz, Juliusberg, Crocker, Colcott Fox and Macleod, while case number two belongs to the purely squamous type and occupies a clinical position between psoriasis and eczema seborrhoicum. It corresponds to Brocq's tenth case, while it differs from the three cases observed by J. C. and C. J. White, which I think correspond to Brocq's third variety.

Pathological Histology

A review of the pathology of parapsoriasis shows a marked and unexpected uniformity in the findings, no matter under

which of several clinical designations the individual cases are described.

Review of the Changes Noted in the Literature:

The two cases described by Unna, Santi and Pollitzer² in 1890 as *parakeratosis variegata* showed epidermal changes of which the most important were the presence of nuclei in the thickened horny layer, dilatation of the intercellular channels of the prickle layer and distension of the nuclear spaces in the prickle and palisade layers, and a general thickening of the epidermis. In both cases the granular layer was present, but the description leads one to believe that it was not so well developed as normal. The superficial portion of the corium showed marked capillary dilatation and a pericapillary infiltration by round cells which the authors consider of connective tissue origin.

In Pinkus' case⁶ of "*psoriasiformem und lichenoidem Exanthem*" there were areas of thickened, nucleated horny layer alternating with non-nucleated areas. The histological description deals chiefly with these superficial changes and little is said of other epidermal changes. The papillae were thickened, shortened and somewhat flattened. About the deeper vessels of the corium there was present an infiltration by small round cells. According to Pinkus the infiltrating cells present in the papillae and in the epidermis were polymorphonuclear leukocytes.

In Juliusberg's cases⁵, published in 1899 under the designation *pityriasis lichenoides chronica*, the stratum corneum was nucleated, not thickened, and formed a scale upon the surface. He gives few details of the changes in the epidermis, but states that the most marked change was present in the corium. Here there were bands of infiltration along the blood vessels, more marked in the papillae than in the deeper corium. The infiltration was composed of mononuclear and polymorphonuclear cells, among which were plasma and mast cells in considerable numbers. The vessel lumina were not compressed. He concludes from his microscopic study that the lesion is produced by a combination of two processes, a parakeratosis and a very superficially situated, slight, inflammatory process. He thinks it impossible to decide which of these is primary or more essential,

but seems to feel that the inflammatory process is not the primary condition.

J. C. White¹⁰ in 1900 gave a detailed description of the changes present in lesions from two cases which were placed under Brocq's erythrodermie pityriasique en plaques disseminées. Here, again, the striking feature was the oedema of the papillae and of the epidermis. The stratum lucidum was absent in both cases and the stratum granulosum was abnormal and in places entirely wanting. In one case the horny layer was thinner than normal, in the other the thickness varied greatly. In both, the superficial layer contained no nuclei. This absence of nuclei in the horny layer is the chief point in which White's cases differ from those described by Unna, Santi and Pollitzer, by Pinkus and by Juliusberg. White considered the infiltrating cells about the dilated capillaries of the corium to be lymphocytes.

Colcott Fox and Macleod¹ in 1901 described in great detail the changes in a case of parakeratosis variegata. Their summary deserves repetition:

“1—Dilatation of the sub-epidermal capillaries.

2—Flattening of the papillary body.

2—Œdema affecting the fibrous stroma near the dilated vessels.

4—Œdema and rarefaction of the collagen; stains badly.

5—Elastin does not stain well.

6—Infiltration of small cells like lymphocytes with a few polynuclear leukocytes among them. Neither plasma cells nor mast cells found.

7—Thinning of the overlying epidermis.

8—Interepithelial œdema and presence of leukocytes.

10—Œdema of the granular cells; occasional absence of them.

11—No stratum lucidum detected.

12—Stratum corneum showing tendency to desquamate.

13—Only here and there could imperfectly cornified cells be found retaining nuclear remains.

14—Where these latter cells were present the granular layer was deficient.”

Brocq's paper of 1902,¹⁶ “Les Parapsoriasis,” gives no histological data, but concludes that under parapsoriasis are to

be included a number of closely related clinical conditions. His paper of 1903¹⁸ comes to the same conclusions and says that certain histological changes are common to the entire group. "Histologically this group is characterized by an infiltration of round cells about the dilated capillary vessels, by a flattening of the papillæ and a marked tendency to their disappearance; by a marked œdema of the upper layers of the derma, and of the epidermis; by an almost complete disappearance of the germinative layer; by a dilatation of the intercellular spaces in the prickly layer; by an œdema of the granular layer which is wanting in places; by the absence of the stratum lucidum; and by the absence of nuclei in the horny layer, except over places where the germinative layer is absent—at these points the nuclei persist in the horny cells."

Bucek¹⁹ in 1903 reached the same conclusions as did Brocq, namely, that despite the clinical variations in the group there are, histologically, more points of resemblance than there are of difference. Histologically the group is characterized by the presence of an inflammatory process of medium grade involving the epidermis and the upper part of the cutis.

C. J. White's case¹⁵ of erythrodermie pityriasique en plaques disseminees, published in 1903, showed changes very much like those present in the two cases of J. C. White¹⁰. The horny layer contained no nuclei, the stratum lucidum was absent and the stratum granulosum was abnormal and in places absent. The papillæ and the epidermis were œdematous.

It will be noted that, no matter what is the clinical nomenclature used, the lesions described by the various authors reviewed above have in common a marked condition of œdema of the epidermis and of the papillæ, absence of the stratum lucidum, well-marked dilatation of the papillary capillaries, and a moderate degree of infiltration by small round cells. The only point about which there is a difference of opinion is the presence or absence of nuclei in the horny layer. In the cases of erythrodermie pityriasique en plaques disseminées, two of J. C. White¹⁰ and one of C. J. White,¹⁵ the stratum corneum contained no nuclei and the stratum granulosum was more or less incomplete. In the cases of parakeratosis variegata of Unna, Santi and Pollitzer² and in the case of pityriasis lichenoides chronica of Juliusberg⁵ the stratum corneum was nucleated.

Colcott Fox and Macleod's¹ case of parakeratosis variegata and Pinkus' case⁶ of "psoriasiformem und lichenoidem Exanthem" occupy an intermediate position, as regards the presence of nuclei in the horny layer, between the cases of Unna, Santi and Pollitzer and of Juliusberg on the one hand, and those of J. C. White and C. J. White on the other. That the persistence of nuclei in the horny layer is a matter of secondary importance and that it is dependent upon the degree of œdema will be shown later. I think that one must, therefore, agree with Brocq and with Bucek in their conclusions that the conditions included in the parapsoriasis group have much in common—that, histologically, the points of resemblance between erythrodermie pityriasique en plaques disseminees, parakeratosis variegata, pityriasis lichenoides chronica and "psoriasiformem und lichenoidem Exanthem" are more numerous and more important than the points of difference.

From the pathological standpoint the chief points at issue may be stated as follows: Are the histological changes found in the various clinical conditions grouped together under parapsoriasis uniform enough to permit of pathological grouping? Is the presence or absence of nuclei in the horny layer of sufficient importance to enable one to subdivide the group? What is the relationship of the epidermal changes to the œdema? What causes the capillary dilatation and the œdema? What is the sequence of events which leads to the fairly uniform microscopic picture presented by the various members of the group under consideration? In what way do the changes described differ from those found in psoriasis, in lichen and in seborrheic eczema? The case to be described will help to elucidate a number of these points.

The published reports give one little help in arriving at an explanation of the manner in which the changes described were produced. All of the authors have concerned themselves chiefly with the changes occurring in the epidermis. They devote little attention to the possibility of involvement of the deeper corium, or briefly state that the deeper layers of the corium were normal. Brocq¹⁶ believes that the pathogenesis of parapsoriasis is the same as that of psoriasis. His statement, that in the members of the parapsoriasis group we are dealing with simple modes of cutaneous reaction, special to certain individ-

uials, permitting the development of the lesions from slight causes of the greatest diversity, is too ingenuous to shed much light upon the subject. Only in C. J. White's report¹⁵ does one find anything which would help one to explain the production of the lesions. His patient had an obliterating arteritis involving the arterioles and sparing the larger arteries. This condition had led to gangrene of a toe. The changes found in the case to be described show that C. J. White did not overestimate the importance of these vascular changes when he concluded his paper with the following questions: "Is not the intercurrent of this strange arteritis of the arterioles of the toe a significant fact in relation to the general cutaneous disease? In other words, have we not here a possible or even probable clue to the genesis of the whole process?"

Our first case, the clinical side of which has been given in the first portion of this paper is important, because the microscopic findings are such as to help explain the production of the changes previously described by other observers, and because the several lesions removed show changes similar in character but varying in degree. This variation in the intensity of the involvement helps to explain certain of the differences that have been noted in the various clinical conditions grouped together under parapsoriasis. Five lesions were removed and examined microscopically. Of these, one shows changes which are apparently somewhat earlier than have been previously noted, another shows a more intense degree of involvement than has been reported, while the remaining three are much like each other and show changes like those described by other writers.

DESCRIPTION OF HISTOLOGICAL FINDINGS.

A: Lesion Showing Earliest Changes:

Epidermis: In the lesion showing the most recent change (Figure 1) one finds at the margins normal epidermis covering normal cutis. The horny layer (a, Figure 11A) in this normal marginal zone averages seven lamellae in thickness and contains no nuclei. The stratum lucidum (b, Figure 11A) is one cell thick, in places two cells thick, non-nucleated, the gran-

ules fine and very numerous. The stratum granulosum (c, Figure 11A) is in most places two cells thick, the cells being filled with granules of rather larger size than those in the layer above. The nuclei of the stratum granulosum are shrunken, irregular in outline and, as a rule, deeply stained. The stratum spinosum is eight to twelve cells thick. Some of the nuclei of the uppermost layer (d, Figure 11A) begin to show the alterations present in the nuclei of the stratum granulosum. The thickness of the epidermis, in the region described, is seventy-nine micra over the papillae and one hundred and thirty-eight micra between the papillae.

As one approaches the area of greatest change one comes upon a zone in which the stratum lucidum has disappeared. A nucleus in this region shows any evidence of loss of fluid and contains pale, much flattened nuclear remnants, which lie in rather wide perinuclear spaces. The number of lamellæ is smaller than normal, although the thickness of the stratum corneum here is about the same as over the normal skin. The granular layer (c, Figure 11B) is composed of a single layer of cells, whose nuclei do not show so marked a degree of condensation as in the normal epidermis. The nuclear spaces are dilated. Beneath the granular layer the prickly layer (d, Figure 11B) shows considerable œdema of the intercellular channels and some dilatation of the nuclear spaces. Only an occasional nucleus in this region shows any evidence of loss of fluid and consequent condensation. The middle point of the region illustrated by Figure 11B is only one hundred and ten micra distant from the marginal normal epidermis shown in Figure 11A.

In the region showing the greatest amount of involvement (Figure 11C) both the stratum lucidum and the stratum granulosum are entirely wanting. The stratum corneum (a, Figure 11C) varies in thickness and the individual lamella are so swollen as to be spindle shaped. The nuclei are rich in fluid and contain considerable chromatin. In the upper portion of the prickly layer (d, Figure 11C) many of the nuclei show irregularities in shape. The nuclear and intercellular spaces are dilated. Deeper down in the stratum spinosum (Figure 12) the œdema becomes very marked. The individual cells are widely separated from each other. The intercellular protoplasmic processes persist as long, fine strands spanning the

much dilated channels (a, Figure 12). An increase in the amount of fluid in the perinuclear spaces has led to a distension of these spaces. In those cells in which this dilatation is most marked, and about which there is œdema of the intercellular spaces, the cytoplasm is represented by a narrow band of compressed, deeply stained material which has a fibrillated appearance. In such cells the nuclei may also show evidences of compression. They are irregular in shape (b, Figure 12) and stain more deeply than normal. Lymphocytes (c, Figure 12) are present in small numbers in the dilated intercellular channels. The stratum mucosum (a, Figure 13) in this more intensely involved area is composed of a single layer of low cylindrical cells. In this layer œdema has also led to distension of the nuclear spaces, to dilatation of the intercellular channels and to vacuolization of the cytoplasm. Many of the nuclei are flattened and stain rather deeply. In the stroma of the papillæ, just beneath the palisade layer, there is a row of fluid filled spaces (b, Figure 13). In spite of the œdema an occasional mitotic figure is seen.

The central point of the area shown in Figure 11C is only fifty-eight micra distant from the center of Figure 11B, and one hundred and sixty-eight micra from the normal epidermis shown in Figure 11A. Figures 12 and 13 are from the same region as Figure 11C. Here the epidermis is fifty-eight micra thick over the papillæ, and one hundred and fifty-five micra thick between the papillæ. As compared with the normal epidermis there has been a thinning of the epidermis over the papillæ and some increase in interpapillary thickness, the latter in spite of an actual decrease in the number of cells. The thinning over the papillæ is due to the disappearance of the granular layers and to a decreased production of cells, whereas the increased thickness between the papillæ is due to the inter- and intra-cellular œdema. The œdema may be so marked as to lead to the formation of minute, microscopic vesicles beneath the horny layer (Figure 1).

Corium: In that region of the most recent lesion which shows the greatest amount of change, the papillæ are swollen and increased in diameter. The capillaries are dilated, and the stroma of the papillæ is almost disorganized by extensive œdema (Figure 2). Young, spindle-shaped, connective tissue

cells are present, as are also lymphocytes. An occasional polymorphonuclear leukocyte is also seen. Deeper down in the corium there are also evidences of œdema. The collagen fibers are swollen, they stain more faintly than normal, and their nuclei are compressed and few in number. The elastic fibrils are widely separated by the œdema and are very fine. The vessels of the deeper corium show certain changes which will be considered in detail in the description of the next section.

B: Lesion Showing Most Advanced Degree of Involvement.

Epidermal Changes: Sections from the lesion showing the most marked change (Figure 3) shows certain changes which have not heretofore been described. From a small central area of this lesion the epidermis has entirely disappeared, leading to the formation of a microscopic ulcer. At the margins of this superficial ulceration the epidermal cells are closely packed together and their nuclei are compressed and deeply stained. The cytoplasm is granular, deeply stained and structureless. The margins of the ulcerated area show no evidence of acute inflammatory change. Beyond the marginal zone the epidermis shows all the changes described in the first lesion, but to a more marked degree. The œdema is so marked that the nuclei are often compressed into deeply stained crescents lying at the margins of greatly distended nuclear spaces.

Changes in the Corium: At the base of the ulcerated area (Figure 4) the collagen fibers are broken and granular. Both the connective tissue and the lymphocyte nuclei are pyknotic and fragmented. Papillæ are entirely wanting in this area. The papillæ at the margins of the ulcerated area show, even to a more marked degree, the capillary dilatation and the interstitial œdema mentioned above. These changes have transformed the tissue of the papillæ into a large meshed network of wide capillaries and connective tissue fibers (Figure 14). Lymphocytic infiltration is more marked in this lesion than in the one first described. In the palisade layer (c, Figure 14) the œdema has led to the formation of very large, fluid-filled nuclear and intercellular spaces (d, e, Figure 14).

In the observations of others, the œdema of the epidermis and of the papillæ receives a large measure of attention. In our case, also, it is so striking as to lead one at once to think of the possibility of changes in the lymphatics of the corium.

Except for slight swelling of the endothelium and a moderate dilatation of the lumina the lymphatics appear normal (Figure 8).

In all the sections of all the lesions removed the blood vessels of the deeper corium are unduly prominent. With a low magnification (150 diameters) the vessels appear as very cellular areas scattered about in the corium beneath the epidermis showing the most marked change (Figure 3). The earliest vascular change to be seen is an increase in the size and in the number of the endothelial cells (Figure 5). The endothelial hypertrophy and hyperplasia are limited to the rather wide, thin-walled venules of the corium, although the arterioles show a certain amount of endothelial swelling. The changes in the endothelium of the veins soon become associated with perivascular inflammatory changes, which manifest themselves by a proliferation of connective tissue with the formation of young fibroblastic cells and by an infiltration of small mononuclear leukocytes (Figure 6). No plasma cells are present in the areas of perivascular inflammation. The end result of the combination of endothelial hypertrophy and hyperplasia with perivascular proliferation and infiltration is a complete obliteration of the lumina of the veins (Figures 4 and 7).

In sections from the lesion showing the most marked involvement (Figure 3) the nerves of the corium are unusually well seen because of their increased size. Nerve bundles so superficially situated as two hundred micra beneath the lower surface of the epidermis may have a diameter of forty micra (Figure 9). A transverse section at almost any plane through one of these swollen nerves shows four or more nuclei of the sheath of Schwann and an undue amount of internuclear tissue. The nerve bundles are surrounded by dilated, fluid-filled spaces. Changes of the nature described are seen only in sections from the most intensely involved lesion.

C: Oldest Lesion.

The remaining lesions excised and studied show changes neither so early as those described in the first lesion nor so intense as those described in the second. They show, of course, a certain amount of variation, but in general seem to be more of the type of lesion which has been described in the literature.

Epidermis: The epidermis is considerably thickened, the

actual thickness being often difficult to determine because of the partial separation and splitting of the horny layer. The thickening is due partly to a general increase in the thickness of the prickle cell layer and partly, in places, to a marked increase in the thickness of the horny layer (Figure 10).

The stratum corneum, in places, is composed of wavy lamellæ, often partially separated from each other. As a rule, the nuclei are visible as elongated, very thin, much compressed and deeply stained bands (Figure 15A). In the deeper portions of the greatly thickened areas of horny layer the individual lamellæ are unusually thick and their nuclei are not so compressed as in the more superficial portions (Figure 15B). The internuclear substance of these thickened lamellæ has a granular appearance, due to the presence of innumerable minute vacuoles.

The stratum lucidum is entirely wanting. The absence of cells of the stratum granulosum type is not complete. Areas in which no granular cells are present alternate with others in which one or two layers of cells of the granulosum type are present. In the latter regions the horny lamellæ are non-nucleated. It is in the areas where no granular cells occur that the thickening of the lamellæ and the persistence of their nuclei are most marked.

The cells of the stratum spinosum are large and the alveolar character of the cytoplasm can be well seen. The intercellular spaces, while readily visible, are not nearly so dilated as in the first lesion described. The majority of the nuclei are pale and vesicular.

The stratum mucosum is composed of cells of a low cylindrical shape, thicker and shorter than in the first lesion described, and with not nearly such marked evidence of œdema. The nuclei are rounded and not so much compressed. Evidences of nuclear division are more numerous than in the early lesion.

Corium: The papillary capillaries are not very prominent and the œdema of the stroma has almost entirely disappeared. Only a few lymphocytes are present, although young connective cells are fairly numerous in the superficial layers of the corium. The papillæ are shorter, thicker and less numerous than normal. Deeper down all the veins of moderate size are completely obliterated and the arterioles also show some com-

pression because of the surrounding inflammatory change. In the areas of perivascular inflammation the prevailing type of cell is the fibroblast, lymphocytes having almost entirely disappeared. No plasma cells are seen.

SUMMARY OF THE HISTOLOGICAL CHANGES.

In briefly summarizing the histological changes described above, it may be said that the epidermis shows the well-marked œdema and the slight lymphocytic infiltration noted by other observers.

In the lesion first described, as one passes from the normal epidermis to that most involved, one notes the disappearance first of the stratum lucidum and then of the stratum granulosum. The lamellæ of the stratum corneum are much thickened and contain nuclear remnants. The papillæ show the marked capillary dilatation and interstitial œdema noted in all previously published descriptions.

In the second lesion described above the changes in the papillæ and in the epidermis have continued to such a degree as to lead to the disappearance of several of the papillæ and of the overlying epidermis. This loss of tissue is not accompanied by the evidences of acute inflammation.

In the oldest lesion capillary dilatation and œdema have largely disappeared. The stratum corneum is much increased in thickness and its lamellæ are nucleated. The persistence of nuclei in the lamellæ and the absence of granular cells occur together in small areas separated from each other by areas in which the horny lamellæ are not nucleated, and cells of the granulosum type are present.

In all the lesions there are changes in the veins of the deeper corium. The cells of the endothelium are increased in size and in number. About many of the veins there is a well-marked zone of lymphocytic infiltration and of connective tissue proliferation. A considerable proportion of the vessels show complete obliteration of their lumina.

In the lesion showing the most marked involvement the nerves of the deeper corium are unduly prominent because of an increase in the tissue of the sheath of Schwann and because of a dilatation of the perineural spaces.

THE PRODUCTION OF THE CONDITION KNOWN AS PARAKERATOSIS.

Unna, Santi and Pollitzer described their cases as parakeratosis variegata, and, according to Unna, parakeratosis is a term applied to the condition in which there results the formation of more or less swollen, nucleated horny lamellæ, which tend to remain united to each other to form scales. Besides these changes in the horny layer, the condition is also characterized by the disappearance of the stratum lucidum and of the stratum granulosum. In order to arrive at an explanation of the production of these changes it is necessary to review the normal process of the cornification of the epidermis.

The work of R. Hertwig and his pupils upon protozoa has established that for every protozoan cell there is a definite relationship between the size of the nucleus and the amount of the chromatin on the one hand, and the size of the cell and the amount of the cytoplasm on the other. Enough work has been done upon the tissue cells of metazoa to indicate that for every type of tissue cell there exists a similar definite relationship. A variety of conditions may alter or upset this normal relationship, but function and nutrition seem to be the most important. If this nucleus-plasma relationship doctrine of R. Hertwig is applied to the cornification of the epidermis the process is one, not of specialization and differentiation, but of gradually progressing physiological degeneration which leads ultimately to cell death. While the horny lamellæ of the epidermis have a protective action, this function is a purely mechanical one. It seems safe to assume that the only active functions possessed by any of the epidermal cells are nutrition and multiplication in the cells of the deeper layers. As the cells approach the surface, even these functions become gradually lost. As the cells become pushed away from the underlying tissue of the corium they lose first the power to divide and then the power to assimilate. As the distance of the cells from the capillary vessels of the corium becomes increased the cells undergo a gradual loss of fluid. This leads, in the upper prickle cell layer, to condensation of the cytoplasm and to shrinking and hyperchromatism of the nuclei. These changes, in addition to the loss of the ability to assimilate, lead to a dis-

turbance of the normal nucleus-plasma relationship. This upset leads to an extrusion of chromatin from the nucleus, and there result compressed cells filled with scattered chromatin granules and containing nuclei poor in chromatin—the cells of the stratum granulosum. A continuation of the process leads to still further chromatin extrusion, the nucleus disappears entirely, and there are formed the cells of the stratum lucidum type. Associated with these changes in the distribution of the chromatin are gradually increasing solidification and degeneration of the cytoplasm. The combined cytoplasmic and nuclear changes are merely the evidences of a gradually progressing physiological degeneration which leads ultimately to death. The final death of the cell is manifested by the complete breaking down of the distributed chromatin and the transformation of the cell into a dried, non-nucleated, horny lamellæ.

If this conception of the normal process of cornification is accepted the explanation of the production of parakeratosis (the term being used here in Unna's sense to describe the epidermal changes and not as a clinical designation) becomes comparatively simple. Common to all the published descriptions of parapsoriasis are the dilatation of the capillaries of the papillæ and the œdema of the papillæ and of the epidermis. These same changes are well marked in our cases. It is these changes which lead to a disturbance of the normal mechanism of cornification and to the production of the phenomena of parakeratosis. Because of the œdema, the epidermal cells do not undergo their normal gradual dessication, and they probably retain the ability to assimilate longer than normal. The upset of the nucleus-plasma relationship, as it occurs in the normal epidermis, does not occur in its regular way and with its regular succession of events. The cells, which in a normal epidermis become gradually dessicated and filled with extruded chromatin to form the stratum granulosum and the stratum lucidum, retain fluid. The relationship between nucleus and cytoplasm is not upset to such an extent as occurs in the normal granulosum and lucidum cells, and chromatin is not extruded from the nuclei. No cells of the normal granulosum or lucidum types are, therefore, produced. When, finally, the cells do reach the surface, they undergo a rather rapid and incomplete dessication which leads to the formation of dead, swollen,

nucleated, horny lamellæ. The variations in the condition of parakeratosis which have been noted in the literature, that is, the incomplete absence of both the granulosum and lucidum layers and amount of œdema the more complete will be the disappearance of the granulosum and lucidum layers and the more prominent will be the nuclei of the horny layer. If the œdema is less intense there will occur in the epidermal cells changes more nearly approaching the normal process of cornification, with the resulting formation of non-nucleated horny lamellæ or the persistence of an irregular stratum granulosum.

THE COURSE OF EVENTS IN THE PRODUCTION OF THE CHANGES FOUND.

A study of the lesions which have been described in detail above seems to give one the succession of events which has led to the changes noted. The parakeratosis, as already stated, is the result of the papillary and epidermal œdema. This latter, in turn, is caused by the capillary dilatation. The distension of the capillaries must be considered an obstructive passive congestion, due to changes in and about the deeper veins of the corium. The vascular involvement must be considered the primary and basic change. This begins as an endothelial hypertrophy and hyperplasia. Perivascular infiltration and proliferation soon follow. The combination of changes within and about the vessels leads to narrowing and to final complete obliteration of the lumina of the veins. The arterioles may show endothelial swelling, but this occurs only after the periphlebitis is well marked. That the vascular changes may be secondary merely evidences of the varying degree of œdema. The greater the formation of non-nucleated horny lamellæ—in other words, variations in the condition which lead to an approach to the normal—are to the changes present in the nerves of one of the lesions appears improbable, since the involvement of the nerves is seen only in the lesion which shows most marked vascular change and is not seen in the early lesion. The involvement of both the vessels and the nerves must be considered the result of some pathological process acting upon both.

The beginning of the process is seen in the first lesion

described. In the second lesion the intensity of the change has led to a loss of tissue, the result of the marked vascular obliteration and consequent œdema.

In the third lesion described it would seem that one is dealing with an attempt at repair. The capillary dilatation has largely disappeared and the interstitial fluid is greatly decreased. Although almost all the veins are obliterated, this attempt at a return to normal must be due, in part, to the establishment of a collateral capillary circulation. The blood supply is still abnormal, but the return of the area to a circulation approaching the normal has led to a decrease of the interstitial œdema, and to a consequent approach toward the normal process of cornification on the part of the epidermis. Hence there is the formation of an incomplete stratum granulosum. The production of such a greatly increased horny layer as is shown in Figure 10 must be due partly to an increased food supply and a resulting hyperplasia. As already stated, mitotic figures are fairly numerous in the deeper epidermal layers of this lesion. A progressive process has become associated with the regressive change which initiated the lesion.

From the above remarks it will appear that the vascular involvement is considered the essential change, and that it is the cause of all the changes in the papillæ and in the epidermis. Such a conclusion has not been met with in the literature reviewed, and there naturally arises some question as to the constancy of its application and as to the possibility of the occurrence of similar involvement in previously described cases. Most of the observers have confined themselves to a description of the changes in the papillæ and in the epidermis. In the majority of the published reports no mention is made of the deeper vessels of the corium. Pinkus⁶ mentions the occurrence of a small round-celled infiltration about the vessels. A study of his diagrammatic illustrations leads one to believe that the vessels must show a considerable amount of involvement. Juliusberg⁵ also mentions the presence of infiltrating cells along the blood vessels. In the two cases reported by J. C. White¹⁰ no vascular abnormalities are mentioned. In the illustrations accompanying the report the deeper vessels of the corium appear unduly prominent, in spite of the low magnification used. To C. J. White¹⁵ belongs the credit of having first

called attention to the possibility of the relationship of vascular changes to the skin lesions. It would seem, therefore, that vascular involvement is one of the most characteristic things in the histological picture of parapsoriasis. It is certain that such a change would explain the capillary dilatation and the œdema which have been noted in all the cases studied histologically. If one excepts the mention of the possibility of changes in the vessels by C. J. White the literature gives no adequate explanation of the production of the more superficial changes so uniformly met with in the descriptions given by previous observers.

CONCLUSIONS AS TO THE PATHOLOGICAL HISTOLOGY.

A review of the literature and the study of the case here reported lead to agreement with the conclusions reached by Brocq¹⁸ and by Bucek¹⁹ that the various members of the parapsoriasis group show many points of similarity.

There are, of course, some variations. These refer chiefly to the completeness of the absence of granular cells and to the presence of nuclei in the horny lamellæ. Such differences as have been noted can all be adequately explained by the varying degree of œdema present. The differences are not so essential as to permit a subdivision of the group. All the variations noted may be present in a single case, as in the one reported here. The first lesion shows changes most like those described by Unna, Santi and Pollitzer and by Juliusberg. The oldest lesion is, in general, much like that described by Pinkus, and it shows the variations noted by Colcott Fox and Macleod in their case. Some areas answer the descriptions given by J. C. White and by C. J. White. The occurrence of ulceration in one of the lesions of our case is not sufficient to give the case a position by itself. The ulcer is of microscopic dimensions, it was not noticed before the excision of the lesion, and it is extremely likely that similar losses of epidermis so slight as not to be seen by the naked eye may have been present in at least one of the lesions in every case heretofore reported. The mere fact that such a condition was not seen in the single lesion studied from each of the cases reported cannot be considered evidence of very much weight. It must be borne in mind, also,

that the ulcer in our case is not associated with any acute inflammatory changes, but is the logical final result of the pathological process which produces the other epidermal changes which have been described.

If future investigations shall confirm the occurrence of vascular involvement in lesions showing the other changes so uniformly noted in parapsoriasis the condition will be well characterized pathologically. Leaving out of consideration the deeper vessels of the corium, parapsoriasis must be considered a condition marked by changes of degenerative and regressive character. In true psoriasis the dilatation of the capillaries may be as marked as in parapsoriasis. But in the former the dilatation is an active one—whether nervous in origin is beside the question—and it does not lead to the intense œdema with the resulting degeneration of epidermal cells and the disturbance of cornification. As compared with parapsoriasis, the process in true psoriasis must be considered progressive in nature, leading to epidermal hyperplasia. In seborrheic eczema and in lichen the pathological process is an acute inflammatory one, characterized by the presence of polymorphonuclear leukocytes. From these various conditions, with which parapsoriasis may show the greatest clinical resemblance, the latter is readily enough differentiated by means of the microscope.

The cases herein reported are important because they help to explain the production of the epidermal changes. In C. J. White's case, obliterating arteriolitis led to gangrene of a toe. Because of the vascular involvement parapsoriasis becomes of clinical importance not only to the dermatologist but also to the internist, since there is no *à priori* reason why similar vascular changes may not occur in the internal organs. The involvement of the deeper vessels of the corium may, perhaps, explain the persistence of the lesions in spite of all treatment, a condition which helps to differentiate parapsoriasis from psoriasis clinically.

DESCRIPTION OF PLATES.

PHOTOMICROGRAPHS.—Figures 1 to 10.

PLATE VIII.

Figure 1.—Earliest Lesion. X 150. Œdema of papillæ. Œdema of epidermis.

Fig. 2.—Earliest Lesion. X 575. Summit of an œdematous papilla. Separation of stroma of papilla. Lymphocytic infiltration and connective tissue proliferation.

PLATE IX.

Fig. 3.—Lesion showing most marked involvement. X 150. Destruction of papillæ and of overlying epidermis. Changes in the vessels and nerves of the corium.

Fig. 4.—Same Lesion as Fig. 5. X 350. Base of ulcerated area.

Fig. 5.—Same Lesion as Fig. 3. X 350. Venule of corium. Hypertrophy and hyperplasia of endothelium.

PLATE X.

Fig. 6.—Same Lesion as Fig. 3. X 350. Venule of corium. Hypertrophy and hyperplasia of endothelium. Perivascular infiltration and proliferation.

Fig. 7.—Same Lesion as Fig. 3. X 350. Venule of corium. Endothelial and perivascular involvement leading to complete obliteration of lumen of vessel.

Fig. 8.—Same Lesion as Fig. 3. X 350. Lymphatic of corium.

Fig. 9.—Same Lesion as Fig. 3. X 350. Nerve of corium. Increase in number of nuclei and in amount of internuclear tissue of sheath of Schwann. Dilatation of perineural space.

Fig. 10.—Oldest Lesion. X 100. Some papillary and epidermal œdema. Papillæ shorter and more widely separated than normal. Hypertrophy and desquamation of horny layer. Involvement of vessels of corium.

PLATE XI

DRAWINGS.—Figs. 11A to 15B.—All the drawings were made with a Leitz camera lucida, Leitz 4 ocular and Leitz 1-12 objective, giving a uniform magnification of 1360 diameters.

Fig. 11A.—Earliest Lesion. Superficial portion of normal epidermis at margin. (a)—Stratum corneum. (b)—Stratum lucidum. (c)—Stratum granulosum. (d)—Superficial portion of stratum spinosum.

Fig. 11B.—Earliest Lesion. Superficial portion of epidermis. Disappearance of stratum lucidum. (a)—Stratum corneum, showing nuclear remnants. (c)—Stratum granulosum. (d)—Stratum spinosum.

Fig. 11C.—Earliest Lesion. Epidermis over summit of an œdematous papilla. Disappearance of stratum lucidum and stratum granulosum. (a)—Stratum corneum, showing nuclei and œdema. (d)—Stratum spinosum. Inter cellular œdema and dilatation of nuclear spaces.

PLATE XII.

Fig. 12.—Earliest Lesion. Deeper portion of stratum spinosum. (a)—Dilated intercellular space. (b)—Distended nuclear space with shrunken nucleus. (c)—Lymphocytes.

Fig. 13.—Earliest Lesion. Stratum mucosum and underlying stroma of papilla. (a)—œdematous stratum mucosum. (b)—A row of fluid-filled spaces just beneath the epidermis.

PLATE XIII.

Fig. 14.—Lesion Showing Most Marked Involvement. Summit of a papilla. (a)—Dilated capillary. (b)—Fluid-filled spaces just beneath epidermis. (c)—Stratum mucosum. (d)—Dilated intercellular space containing lymphocytes. (e)—Distended nuclear spaces containing lymphocytes.

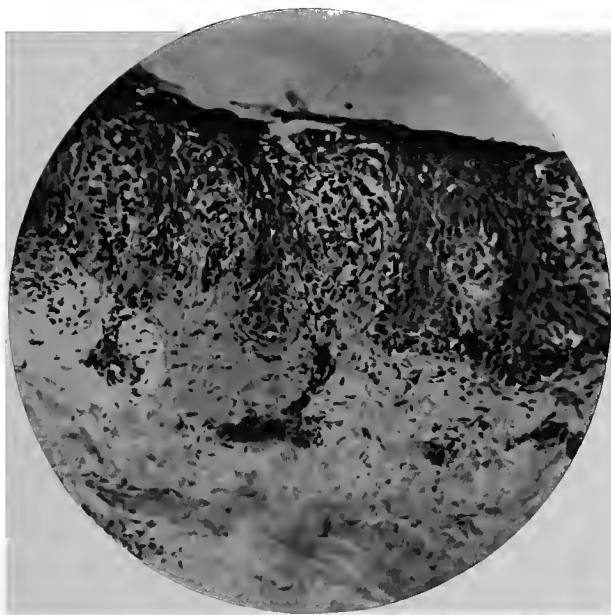


FIG. 1.

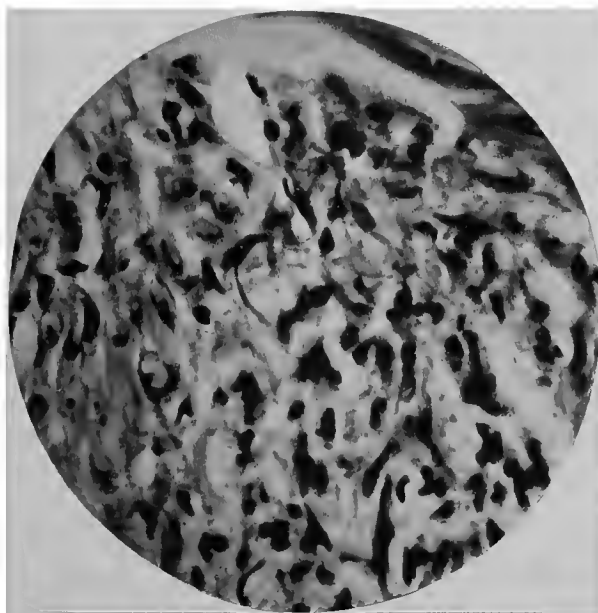


FIG. 2.

PLATE IX—To Illustrate Article by Drs. W. T. Corlett and Oscar T. Schultz.

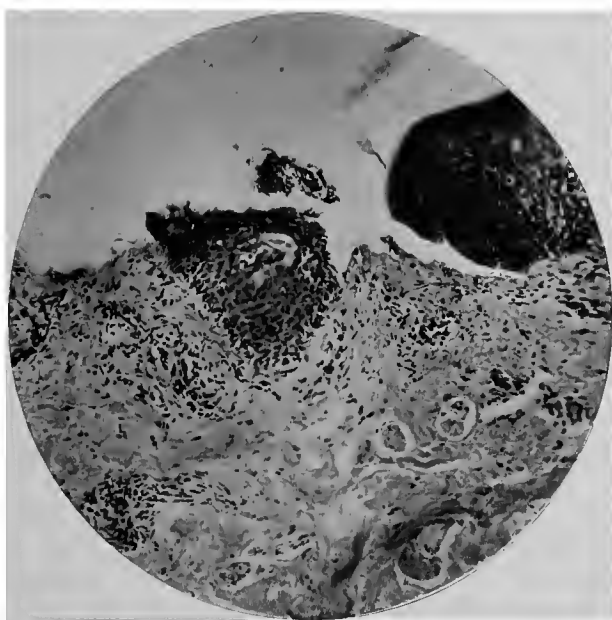


FIG. 3.

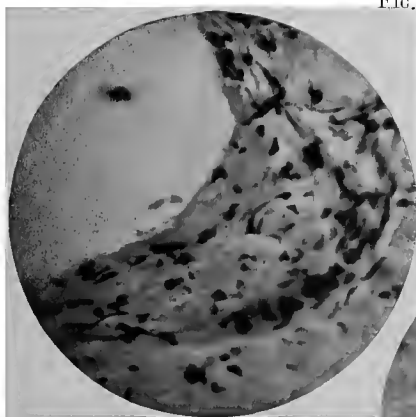


FIG. 4.

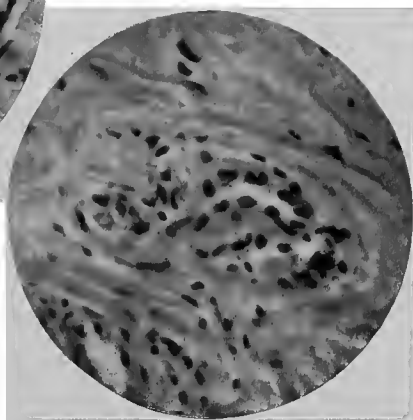


FIG. 5.

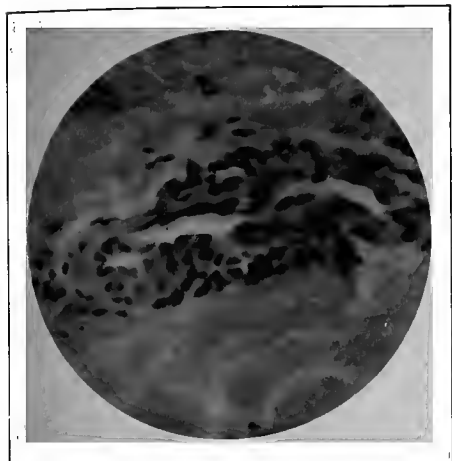


FIG. 6.

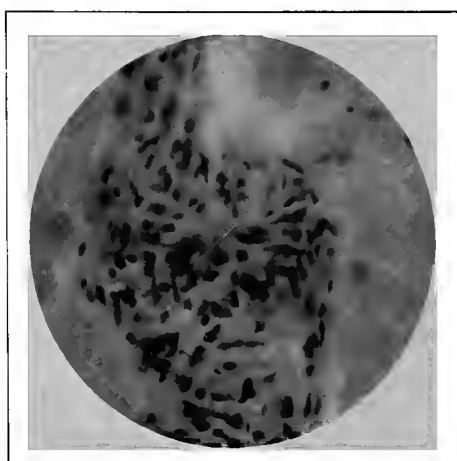


FIG. 7.

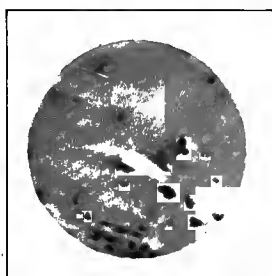


FIG. 8.

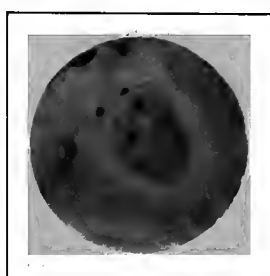


FIG. 9.



FIG. 10.

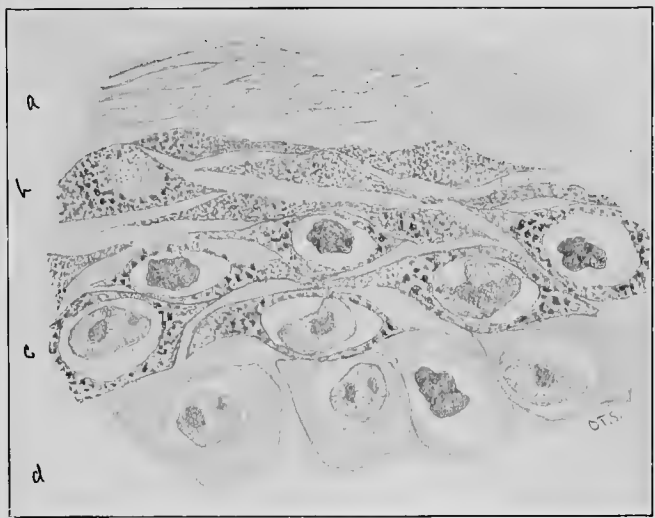


FIG. 11 a.

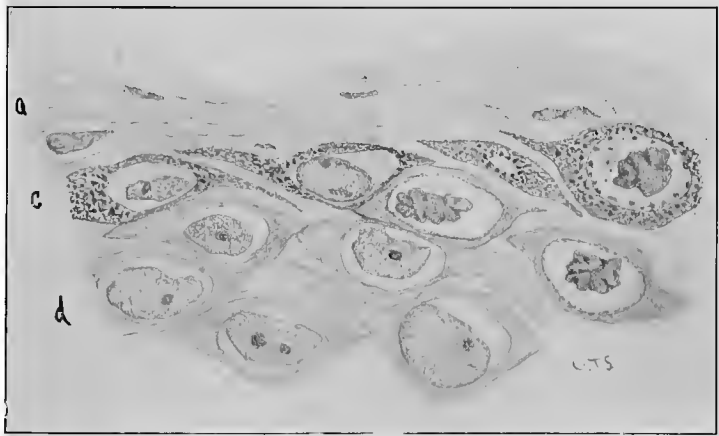


FIG. 11 b.

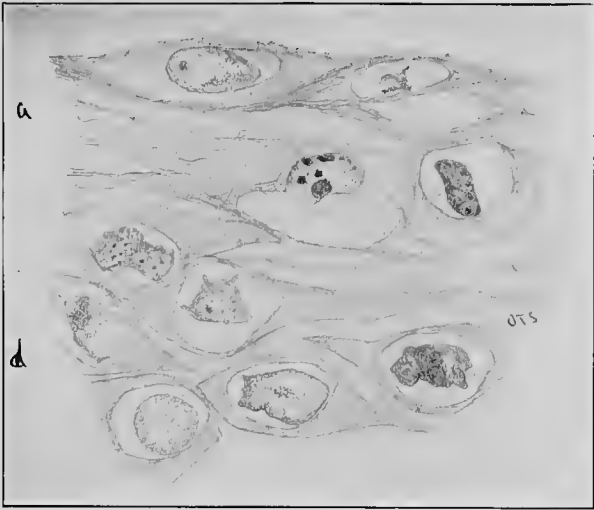


FIG. 11 c.

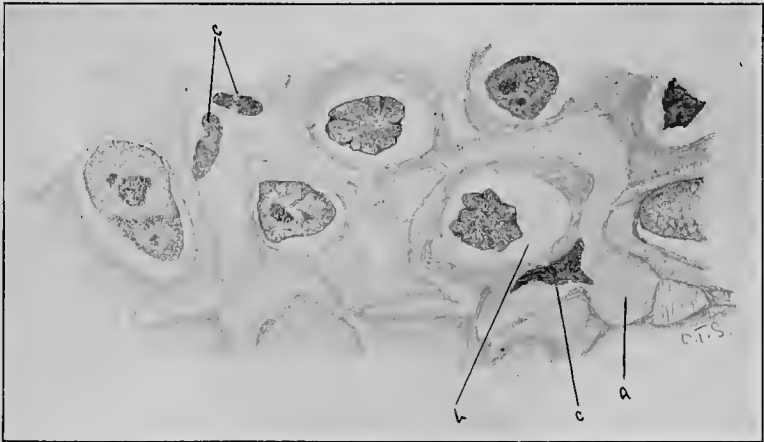


FIG. 12.

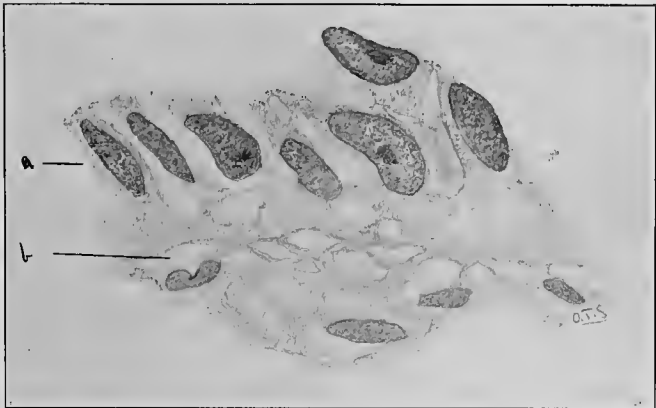


FIG. 13.



FIG. 14.

PLATE XIV—To Illustrate Article by Drs. W. T. Corlett and Oscar T. Schultz.

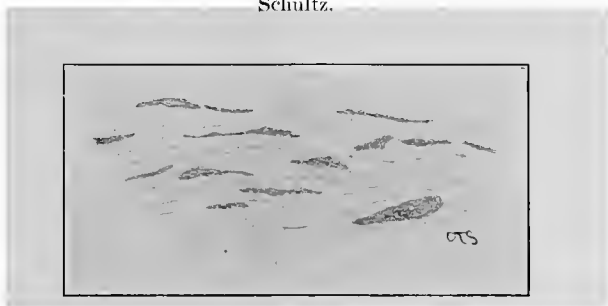


FIG. 15 a.

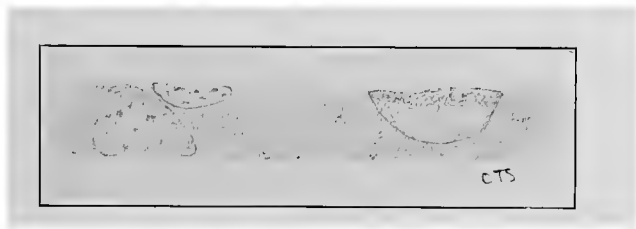


FIG. 15 b.



FIG. 16.

Fig. 15A.—Oldest Lesion. Superficial portion of stratum corneum. Closely placed lamellæ containing compressed nuclei.

Fig. 15B.—Oldest Lesion. Deeper portion of stratum corneum. Swollen, nucleated, vacuolated lamella.

PLATE XIV.

Fig. 16.—Parapsoriasis. Clinical picture of cases.

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